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## **PCT**

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- (57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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## EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

#### Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.

Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mislabeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- $\alpha$ , interferon- $\beta$ , interferon- $\gamma$ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al.,

Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include
sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and
the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5'
coding sequences of genes encoding secretory proteins.

## Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 104-106 fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired
proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the 20 extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEO ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40·140 and 242·377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42·46, 48, 49, 51, 53, 57, 60, 62·73, 76·78, 80·83, 85·88, 90, 93·95, 97, 99·102, 104, 107·125, 127, 128, 130, 132, 134·140 and 242·377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEO ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEO ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEO ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described ~ herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEO ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynoculeotides encoding said polypeptides.

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## **Brief Description of the Drawings**

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Notl. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEO ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEO ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

## **Detailed Description of the Preferred Embodiment**

#### 15 1. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

## A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

#### **EXAMPLE 1**

## Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1  $\mu$ g of RNA was incubated in a final reaction medium of 10  $\mu$ l in the presence of 5 U of T<sub>4</sub> phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2  $\mu$ l of <sup>32</sup>pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH, NaBH<sub>3</sub>CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

## **EXAMPLE 2**

## Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step.

Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+Cap:

25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)

-Cap:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

#### **EXAMPLE.3**

## Coupling of the Dialdehyde with Biotin

5 The oxidation product obtained in Example 2 was dissolved in 50 μl of sodium acetate at a pH of between 5 and 5.2 and 50 μl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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## **EXAMPLE 4**

## **Specificity of Biotinylation**

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.

Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.

Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, 5 chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure. For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment. Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the 15 biotinylated mRNAs from the beads following enrichment.

#### **EXAMPLE 5**

## Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 20 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

## **EXAMPLE 6**

#### Efficiency of Recovery of Biotinylated mRNAs 25

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with 32pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing 30 conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

## **EXAMPLE 7**

## Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula H<sub>2</sub>N(R1)NH<sub>2</sub> at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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## **EXAMPLE 8**

## Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µl of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

## **EXAMPLE 9**

## **Oxidation of Diols**

Up to 1 0D unit of RNA was dissolved in 9 μl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 μl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 μl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10μl or more of water or appropriate buffer and dialyzed against water.

Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

#### **EXAMPLE 10**

## Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

## **EXAMPLE 11**

## Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 µJ of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO<sub>4</sub>/accetone. The pellet was resuspended in 200 µJ of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO<sub>4</sub>/accetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10  $\mu$ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39  $\mu$ l of 10 mM urea and 2  $\mu$ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45  $\mu$ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with <sup>32</sup>P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with <sup>32</sup>P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)
GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6)
dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEO ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEO ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (\_As) oligodeoxyribonucleotides of the 10 pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.

Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.

Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the presence of cDNA.

Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.

Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.

Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.

Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.

Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

## B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

30 groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

#### **EXAMPLE 12**

## Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this 10 procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation eificiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first 15 and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards, supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold 20 Spring Harbor Laboratory Press, 1989.

## II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

#### **EXAMPLE 13**

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## Preparation of mRNA

Total human RNAs or PolyA+ RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by 30 two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe

10 complementary to the oligonucleotide tag.

#### **EXAMPLE 14**

## cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

#### **EXAMPLE 15**

## Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

## **EXAMPLE 16**

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

#### **EXAMPLE 17**

## Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL), BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc. Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn30 helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

Before searching the cDNAs in the NETGENE<sup>TM</sup> database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

## **EXAMPLE 18**

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## **Elimination of Undesired Sequences from Further Consideration**

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNAs. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was 5 used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

## **EXAMPLE 19**

## Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of 15 "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE™ database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends 20 of their corresponding mRNAs, the following analysis was performed.

## **EXAMPLE 20**

## Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs 25 which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit  $\alpha$  and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

#### **EXAMPLE 21**

# Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENE<sup>TM</sup> was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

#### **EXAMPLE 22**

## Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENE<sup>TM</sup> database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENE<sup>TM</sup> contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

#### **EXAMPLE 23**

## Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

#### **EXAMPLE 24**

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## Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAGTM database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAG™ database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the 10 known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG™ database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which 15 extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

## **EXAMPLE 25**

## **Categorization of Expression Patterns**

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail 30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

## **EXAMPLE 26**

## **Evaluation of Expression Levels and Patterns of mRNAs**

## Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the

serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method,

cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene
expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first
restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least
once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding
to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for
hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the
digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the
cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the
5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., *supra*) or synthesized and then
addressed to the chip (Sosnowski et al., *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are
synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

## III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino acids of the sequences of SEQ ID NOs: 40-140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

## **EXAMPLE 27**

## General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENE<sup>TM</sup> database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

## 1. Obtaining Extended cDNAs

## 10 a) First strand synthesis

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5' ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

## b) Second strand synthesis

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A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG-3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G-3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

#### 5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

#### a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

#### b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

#### c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls and validation steps are carried out as described in example 15.

#### 3. Cloning of Full Length Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

# 4. Computer Analysis of Full Length Extended cDNA

Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

- Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ
- 10 (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

### a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

### b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

#### c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

# d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs

10 are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001.

Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

#### 5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

#### a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

#### b) Manual sequence selection

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Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other

#### **EXAMPLE 28**

### Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" of category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at <a href="http://expasy.hcuge.ch/sprot/prosite.html">http://expasy.hcuge.ch/sprot/prosite.html</a>. Prosite\_convert and prosite\_scan programs (http://ulrec3.unil.ch/ftpserveur/prosite\_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite\_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

proteins) was skipped during the search with prosite\_scan. The program used to shuffle protein sequences (db\_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a Tm of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Cilmmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can aiso be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X10<sup>6</sup> dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu$ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X10<sup>6</sup> dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

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1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

#### **EXAMPLE 29**

# Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where
the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is
contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended
cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200
nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as
oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in
SX SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide
containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence
are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a
magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted
into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is
transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony
hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

#### IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

#### 30 EXAMPLE 30

#### Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEO ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA... Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

20 It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEO ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus. claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5'primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with Bglll, purified and ligated to pXT1, now containing a poly A signal and digested with Bglll.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as CDS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

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the chimera. The other half of the chimera may be  $\beta$ -globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to  $\beta$ -globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the  $\beta$ -globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

10 (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express<sup>TM</sup> Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

#### **EXAMPLE 31**

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the
cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an
unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein
bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled
protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

#### 5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is

10 beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 33**

#### Assaying the Proteins Expressed from Extended cDNAs or Portions

## 15 <u>Thereof for Activity as Immune System Regulators</u>

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins ercoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 20 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β2 macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 34**

# <u>Assaying the Proteins Expressed from Extended cDNAs</u> or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 35**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of 30 nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle

(smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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#### **EXAMPLE 36**

# <u>Assaying the Proteins Expressed from Extended cDNAs or Portions</u> <u>Thereof for Regulation of Reproductive Hormones or Cell Movement</u>

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 36A**

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# Assaying the Proteins Expressed from Extended cDNAs or

# Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

#### **EXAMPLE 37**

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# Assaying the Proteins Expressed from Extended cDNAs or

#### Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 38**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

#### **EXAMPLE 38A**

#### Assaying the Proteins Expressed from Extended cDNAs or Portions

#### Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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#### **EXAMPLE 38B**

#### Assaying the Proteins Expressed from Extended cDNAs or

## Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### **EXAMPLE 39**

# Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes.

30 The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase.

5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

#### **EXAMPLE 40**

## Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

# A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

#### B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12  $\mu$ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as 15 described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic 20 compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

# V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable 25 therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

#### **EXAMPLE 41**

# Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a 30 variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with 5 dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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#### **EXAMPLE 42**

# Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using 15 techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization 25 and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers 30 based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

#### **EXAMPLE 43**

# Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

#### **EXAMPLE 44**

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## Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

#### **EXAMPLE 45**

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#### Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press, pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., <a href="mailto:supra">supra</a>). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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#### **EXAMPLE 46**

## **Dot Blot Identification Procedure**

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P<sup>32</sup> using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

#### **EXAMPLE 47**

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#### Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P<sup>32</sup>. The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species 20 from which a sample is derived as described above.

#### **EXAMPLE 48**

## Identification of Tissue Types or Cell Species by Means of

#### Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that

reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

## A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

## B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55  $\mu$ l, and containing from about 1 to 100  $\mu$ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

## **EXAMPLE 49**

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

#### **EXAMPLE 50**

## Mapping of Extended cDNAs to Human

#### Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a <sup>32</sup>P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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#### **EXAMPLE 51**

## Mapping of Extended 5' ESTs to Chromosomes

#### Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. *Vroc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research

Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated.

Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 x SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at  $\cdot 20^{\circ}$ C are treated for 1 h at 37°C with RNase A (100  $\mu$ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl<sub>2</sub>) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of
biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., supra.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given
chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

#### **EXAMPLE 52**

## Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

#### **EXAMPLE 53**

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

#### VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

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## **EXAMPLE 54**

#### **Construction of Secretion Vectors**

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV4D promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the

extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion 5 protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including 10 retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange 20 chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose-secretion is 25 desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and 30 other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

#### **EXAMPLE 55**

## Use of Extended cDNAs or 5' ESTs to Clone Upstream

#### Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5  $\mu$ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2  $\mu$ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc), and 1  $\mu$ l of the Tth polymerase 50X mix in a total volume of 50  $\mu$ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5  $\mu$ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50  $\mu$ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

#### **EXAMPLE 56**

#### Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase,  $\beta$ galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

#### **EXAMPLE 57**

Cloning and Identification of Promoters

Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

## **EXAMPLE 58**

# Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

## VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

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to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

#### EXAMPLE 59

#### Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom).

The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or

more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10<sup>-10</sup>M to 1x10<sup>-4</sup>M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10<sup>-7</sup> translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., *supra*.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the

effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to
antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

#### **EXAMPLE 60**

#### Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

#### **EXAMPLE 61**

# Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

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#### **EXAMPLE 62**

## Use Of Signal Peptides Encoded By 5' Ests Or Sequences

# Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

#### **EXAMPLE 63**

## Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

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In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEO ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

25

#### **EXAMPLE 64**

## **Functional Analysis of Predicted Protein Sequences**

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 33) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

## 15 A) Proteins which are closely related to known proteins

#### Protein of SEQ ID NO: 217

20

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AFD14955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

## 25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEO ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEO ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEO ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEO ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEO ID NOs: 175 and for positions 94, and 108-110 of the matched protein for the protein of SEO ID NOs: 232. Proteins of SEO ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

## 5 Proteins of SEO ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 : 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

## 20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEO ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

#### Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEO ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

#### Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al., FEBS Lett.*, 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink *et al., Hum. Mol. Gent.*, 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

<u>Proteins of SEQ ID NOs: 149, 150 and 211</u>

The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic*. *Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

## Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders
including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

## Protein of SEO ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-L-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

## Protein of SEQ ID NO: 163

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The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

## C) Proteins homologous to a domain of a protein with known function

#### Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

#### Protein of SEQ ID NO: 225

The protein of SEO ID NO: 225 encoded by the extended cDNA SEO ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369 : 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

## Protein of SEQ ID NO: 153

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The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

## Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

#### Protein of SEQ ED NO: 240

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The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52

30 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEO ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

#### Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

## Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

25 Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

#### Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEO ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

## Protein of SEQ ED NO: 167

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The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEO ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

#### Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

## 25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily.

The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

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# SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

TABLE !

	ABLE	
SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	82
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	81
51		53
52	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
53	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
54	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
56	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
57	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
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76       U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997       136         77       U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998       75         78       U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998       61         79       U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998       61         80       U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997       130         81       U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998       65         82       U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998       78         83       U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998       78         84       U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998       63         85       U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998       65         86       U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997       152	
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121   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   58     122   U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998   72     123   U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998   73     124   U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998   70     125   U.S. Provisional Patent Application Serial No. 60/089,957, filed Dec. 17, 1997   40     126   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   44     127   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   45     128   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   47     129   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   48     130   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   51     131   U.S. Provisional Patent Application Serial No. 60/069,957, filed Nov. 13, 1997   50     132   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   56     133   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   57     134   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   71     135   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   72     136   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   65     137   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   65     138   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   65     139   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   65     139   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   74     140   U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997   75     140   U.S. Provisional Patent Application Serial No. 60/069,957, filed D	120		
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368	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	201
369	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	202
370	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	203
371	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	204
372	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	205
373	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	206
374	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	207
375	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	208
376	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	209
377	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	210

TABLE II: Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S-61 X-16	90	17
tRNA	Fasta	both	•	80	60
rRNA	Blastn	both	S-108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S-144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S=72	70	40
Repeats	Blastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S-108	90	30
ESTs .	Blatsn	both	S=108 X=16	90	30
Proteins	blastxŋ	top	E-0.001		

<sup>\*</sup> use "Quick Fast" Database Scanner

 $<sup>\,\</sup>perp\,$  alignment further constrained to begin closer than 10bp to EST(5' end

 $<sup>5 - \</sup>eta$  using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characte		Selection characteristics			
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both	·	90	15	
tRNA <sup>1</sup>	FASTA	both		80	90	
rRNA*	BLASTN .	both	S-108	80	40	<u> </u>
mtRNA*	BLASTN	both	S-108	80	40	
Procaryotic*	BLASTN	both	S-144	90	40	
Fungal*	BLASTN	both	S-144	90	40	
Alu*	BLASTN	both	S-72	70	40	max 5 matches, masking
L1'	BLASTN	both	S-72	70	40	max 5 matches, masking
Repeats*	BLASTN	both	S-72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal	<u>.</u>	top	AATAAA allowing 1 mismatch			in the 50 nucleotides preceding the 5' end of the polA
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both	•	90	30	
Geneseq	BLASTN	both	W-8, B-10	90	30	
ORF	BLASTP	top	W-8, B-10	•	•	on ORF proteins, max 10 matches
Proteins*	BLASTX	top	E-0.001	70	30	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

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TABLE IV

ld	FCS Location	SigPep Location	Mature	Stop	PolyA Signal	PolyA Site Location
			Polypeptide Location	Codon	Location	
40	7 through 471	7 through 99	100 through 471	Location 472	537 through 542	554 through 568
4.1	168 through 332		168 through 332	333	557 through 562	•
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614	1.	1.
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041	1.	2024 through 2036
46	443 through 619	443 through 589	590 through 619	620	1.	1267 through 1276
47	206 through 747	·	206 through 747	<del> </del>		
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41		21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399		271 through 399	400		
53	103 through 252	103 through 213	214 through 252	253	<del> </del>	588 through 597
54	2 through 460		2 through 460	461	713 through 718	735 through 748
55	31 through 231		31 through 231	232	769 through 774	690 through 703
56	305 through 565		305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206	· -	135 through 206	207	850 through 855	1056 through 1069
59	135 through 818		135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291		1.
61	485 through 616		485 through 616	617		669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758	•	1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1,248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916	•	•	904 through 916
74	62 through 520	•	62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167	•	21 through 167	168		
76	22 through 318	22 through 93	94 through 318	319	497 through 502	516 through 526
77	8 through 292	8 through 118	119 through 292	293	317 through 322	339 through 352
78	16 through 378	16 through 84	85 through 378	379	502 through 507	522 through 542

CONT. TABLE IV

	T. TABLE IV					· _
79	57 through 233	•	57 through 233		·	
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542	•	597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382		89 through 382	383	·	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362	·	
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802	•	199 through 802		780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361	·	26 through 361	· -	·	350 through 361
92	3 through 131	·	3 through 131	132		591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417		327 through 417	1.		404 through 417
97	63 through 398	63 through 206	207 through 398	399		1.
98	2 through 163		2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466		
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295	•	
102	81 through 518	81 through 173	174 through 518	519	-	·
103	66 through 326		66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290		
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318 .	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333		702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563		
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400		
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506		
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770
	<del></del>			L	.1	

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CONT. TABLE IV

121   58 through 1095   58 through 114   115 through 1095   1096   128 through 1213   1202 through 1213   121 through 660   31 through 660   681   1288 through 1213   1307 through 1318   1233   11 through 562   31 through 592   31 through 592   585   585   795 through 821   840 through 531   1233   11 through 585   585   795 through 820   841 through 531   1286 through 821   840 through 531   1286 through 821   840 through 531   1286 through 825   74 through 1285   74 through 1285   174 through 285   174 through 287   174 thro	0011	I. IADEL IV					
122   31 through 502   31 through 90   91 through 502   583   816 through 821   840 through 825     124   15 through 695   15 through 80   81 through 695   696   795 through 800   814 through 826     125   74 through 695   74 through 196   197 through 295   296   545 through 550   561 through 571     126   440 through 659   481 through 281   381 through 871   472 through 877   121 through 281   381 through 282   298 through 477	121	58 through 1095	58 through 114	115 through 1095	1096	1.	1202 through 1213
124   15 through 895   15 through 80	122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
125	123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
126	.124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
127   38 through 283   38 through 85   86 through 283   284   257 through 282	125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
121 through 477	126	440 through 659	-	440 through 659		601 through 606	·
2 through 163   -     2 through 163   164   292 through 297   310 through 323   130   46 through 675   46 through 87   88 through 675   676   1364 through 1369   1383 through 1392   1311   62 through 385   -     62 through 385   386   974 through 979   987 through 999   132   422 through 231   -	127	38 through 283	38 through 85	86 through 283	284	257 through 262	
130	128	121 through 477	121 through 288	289 through 477		•	·
131   62. through 385   - 62 through 385   386   974 through 979   987 through 999     132   422 through 550   422 through 475   476 through 550   551   - 714 through 775     133   124 through 231   - 124 through 475   476 through 550   551   - 714 through 725     134   131 through 1053   131 through 169   170 through 1053   - 1019 through 1024   - 1177 through 1053     135   86 through 403   86 through 181   182 through 403   404   1097 through 1102   1117 through 1128     136   37 through 162   37 through 93   94 through 162   163   224 through 229   243 through 254     137   31 through 381   31 through 90   91 through 381   382   - 875 through 886     138   46 through 579   46 through 156   157 through 579   580   - 875 through 886     139   92 through 471   92 through 172   173 through 471   454 through 459   458 through 849     140   154 through 675   154 through 498   499 through 675   676   819 through 824   338 through 849     242   18 through 173   18 through 498   499 through 675   676   819 through 824   838 through 849     243   17 through 595   17 through 85   86 through 595   596   820 through 825   840 through 851     244   89 through 334   89 through 130   131 through 334   335   462 through 467   484 through 485     245   21 through 674   21 through 88   84 through 674   615   849 through 867   886 through 887     246   94 through 573   94 through 258   259 through 673   574   862 through 867   886 through 887     247   74 through 397   74 through 127   128 through 397   398   472 through 397   396 through 886     248   51 through 602   45 through 107   108 through 602   603   828 through 833   860 through 880     250   45 through 580   24 through 107   108 through 602   603   828 through 833   860 through 880     251   24 through 580   24 through 107   108 through 602   603   828 through 830   860 through 896     252   109 through 595   59 through 596   506   1042 through 107   1062 through 1073     253   128 through 595   59 through 596   59 through 598   59 through 598   59 through 606   6	129	2 through 163	•	2 through 163	164	292 through 297	310 through 323
132   422 through 550   422 through 475   476 through 550   551     714 through 725     133   124 through 231     124 through 231   232     387 through 400     134   131 through 1053   131 through 169   170 through 1053     1019 through 1024     135   86 through 403   86 through 181   182 through 403   404   1097 through 1102   1117 through 128     136   37 through 182   37 through 93   94 through 162   163   224 through 229   243 through 254     137   31 through 381   31 through 90   91 through 381   382     875 through 886     138   46 through 579   46 through 156   157 through 579   580       139   92 through 471   92 through 172   173 through 471     454 through 859   456 through 471     140   154 through 675   154 through 498   499 through 675   676   819 through 824   838 through 849     242   18 through 173   18 through 77   78 through 1595   596   820 through 825   840 through 851     243   17 through 595   17 through 83   86 through 595   596   820 through 825   840 through 851     244   89 through 614   21 through 83   84 through 343   335   462 through 847   484 through 495     245   21 through 614   21 through 83   84 through 614   615   849 through 667   886 through 897     247   74 through 573   94 through 258   259 through 573   574   862 through 867   886 through 897     248   51 through 573   94 through 157   128 through 397   398   472 through 477   507 through 518     248   51 through 602   45 through 107   108 through 602   603   828 through 833   850 through 860     251   24 through 505   59 through 573   274 through 560   561   563 through 107   986 through 860     252   109 through 505   59 through 573   274 through 560   561   563 through 578   563 through 593     254   59 through 505   59 through 573   274 through 555   59   1104 through 1161     102 through 506   59 through 507   59 through 579   506   1042 through 1073     255   1 through 507   1 through 147   148 through 207   208   748 through 598   807 through 618     256   109 through 505   59 through	13D	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
133   124 through 231	131	62.through 385	•	62 through 385	386	974 through 979	987 through 999
131 through 1053   131 through 189   170 through 1053   .   1019 through 1024   .   .   .   .   .   .   .   .   .	132	422 through 550	422 through 475	476 through 550	551	•	714 through 725
135   86 through 403   86 through 181   182 through 403   404   1097 through 1102   1117 through 1128   136   37 through 162   37 through 33   94 through 162   163   224 through 229   243 through 254   137   11 through 381   31 through 391   31 through 381   382	133	124 through 231		124 through 231	232	1.	387 through 400
136         37 through 162         37 through 93         94 through 162         163         224 through 229         243 through 254           137         31 through 381         31 through 90         91 through 381         382         .         875 through 886           138         46 through 579         46 through 156         157 through 579         580         .           139         92 through 471         92 through 172         173 through 471         .         454 through 489         489 through 675         676         819 through 824         388 through 849           242         18 through 173         18 through 471         78 through 173         174         864 through 869         882 through 83           243         17 through 595         17 through 85         86 through 595         596         820 through 825         840 through 861           244         89 through 334         89 through 130         131 through 614         615         849 through 867         484 through 884           245         21 through 614         21 through 83         84 through 614         615         849 through 867         886 through 887           246         94 through 573         94 through 258         259 through 573         574         862 through 867         886 through 867 through 586	134	131 through 1053	131 through 169	170 through 1053		1019 through 1024	
137   31 through 381   31 through 90   91 through 381   382	135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
138	136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
139   92 through 471   92 through 172   173 through 471   -   454 through 459   458 through 471	137	31 through 381	31 through 90	91 through 381	382		875 through 886
154 through 675   154 through 498   499 through 675   676   819 through 824   338 through 849	138	46 through 579	46 through 156	157 through 579	580	•	
242       18 through 173       18 through 77       78 through 173       174       864 through 869       882 through 893         243       17 through 595       17 through 85       86 through 595       596       820 through 825       840 through 851         244       89 through 334       89 through 130       131 through 334       335       462 through 467       484 through 495         245       21 through 614       21 through 83       84 through 614       615       849 through 854       873 through 884         246       94 through 573       94 through 258       259 through 573       574       862 through 867       886 through 897         247       74 through 397       74 through 127       128 through 397       398       472 through 477       507 through 518         248       51 through 242       51 through 116       117 through 242       243       319 through 324       339 through 350         249       111 through 191       111 through 155       156 through 191       192       965 through 333       850 through 860         250       45 through 602       45 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 560       561       563 through 568       583 through 593	139	92 through 471	92 through 172	173 through 471		454 through 459	458 through 471
243       17 through 595       17 through 595       596       820 through 825       840 through 851         244       89 through 334       89 through 130       131 through 334       335       462 through 467       484 through 495         245       21 through 614       21 through 83       84 through 614       615       849 through 854       873 through 884         246       94 through 573       94 through 258       259 through 573       574       862 through 867       886 through 897         247       74 through 397       74 through 127       128 through 397       398       472 through 477       507 through 518         248       51 through 242       51 through 161       117 through 242       243       319 through 324       339 through 350         249       111 through 191       111 through 155       156 through 191       192       965 through 970       986 through 986         250       45 through 602       45 through 602       603       828 through 833       850 through 593         251       24 through 568       109 through 273       274 through 558       559       1104 through 114         253       128 through 835       128 through 835       128 through 835       128 through 836       1145 through 1047       1062 through 1073 <tr< td=""><td>140</td><td>154 through 675</td><td>154 through 498</td><td>499 through 675</td><td>676</td><td>819 through 824</td><td>838 through 849</td></tr<>	140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
244       89 through 334       89 through 130       131 through 334       335       462 through 467       484 through 495         245       21 through 614       21 through 83       84 through 614       615       849 through 854       873 through 884         246       94 through 573       94 through 258       259 through 573       574       862 through 867       886 through 897         247       74 through 397       74 through 127       128 through 397       398       472 through 477       507 through 518         248       51 through 242       51 through 116       117 through 242       243       319 through 324       339 through 350         249       111 through 191       111 through 155       156 through 191       192       965 through 970       986 through 986         250       45 through 602       45 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 358       359 through 835       836       1145 through 1047       1062 through 1073	242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
245         21 through 614         21 through 83         84 through 614         615         849 through 854         873 through 884           246         94 through 573         94 through 258         259 through 573         574         862 through 867         886 through 887           247         74 through 397         74 through 127         128 through 397         398         472 through 477         507 through 518           248         51 through 242         51 through 116         117 through 242         243         319 through 324         339 through 350           249         111 through 191         111 through 155         156 through 191         192         965 through 970         986 through 986           250         45 through 602         45 through 602         603         828 through 833         850 through 860           251         24 through 602         45 through 560         561         563 through 568         583 through 593           252         109 through 558         109 through 835         274 through 835         856         1104 through 1114           253         128 through 835         128 through 835         836         1145 through 1150         1170 through 1181           254         59 through 835         359 through 505         506         1042 through 1047	243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
246         94 through 573         94 through 258         259 through 573         574         862 through 867         886 through 897           247         74 through 397         74 through 127         128 through 397         398         472 through 477         507 through 518           248         51 through 242         51 through 116         117 through 242         243         319 through 324         339 through 350           249         111 through 191         111 through 155         156 through 191         192         965 through 970         986 through 986           250         45 through 602         45 through 602         603         828 through 833         850 through 860           251         24 through 560         24 through 560         561         563 through 568         583 through 593           252         109 through 558         109 through 273         274 through 835         559         -         1104 through 1114           253         128 through 835         128 through 835         359 through 835         836         1145 through 1150         1170 through 1181           254         59 through 505         59 through 505         506         1042 through 1047         1062 through 1073           255         1 through 207         1 through 148 through 207         208	244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
247       74 through 397       74 through 127       128 through 397       398       472 through 477       507 through 518         248       51 through 242       51 through 116       117 through 242       243       319 through 324       339 through 350         249       111 through 191       111 through 155       156 through 191       192       965 through 970       986 through 986         250       45 through 602       45 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 101       102 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 304       12 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 419       201 through 409       101 through 272       273 through 304       104 through 27	245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
248       51 through 242       51 through 116       117 through 242       243       319 through 324       339 through 350         249       111 through 191       111 through 155       156 through 191       192       965 through 970       986 through 996         250       45 through 602       45 through 107       108 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 505       59 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 147       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 272       273 through 304       305       708 through 606	246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
249       111 through 191       111 through 155       156 through 191       192       965 through 970       986 through 996         250       45 through 602       45 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 101       102 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 358       359 through 505       506       1042 through 789       807 through 818         256       12 through 734       12 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 606       627 through 637         260	247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
250       45 through 602       45 through 602       603       828 through 833       850 through 860         251       24 through 560       24 through 101       102 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       .       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 358       359 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 612       628 through 637         260       123 through 419       201 through 302       123 through 37       377 through 673       674       .       1025 th	248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
251       24 through 560       24 through 560       561       563 through 568       583 through 593         252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 358       359 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 147       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 647         269       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 673       98 through 376       377 through 673       674       -       1025	249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
252       109 through 558       109 through 273       274 through 558       559       -       1104 through 1114         253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 358       359 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 47       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 419       201 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 376       377 through 673       674       -       1025 through 1035         262       17 through 463       17 through 232       233 through 463       464       657	250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
253       128 through 835       128 through 220       221 through 835       836       1145 through 1150       1170 through 1181         254       59 through 505       59 through 358       359 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 147       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 673       674       .       1025 through 1035         261       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696	251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
254       59 through 505       59 through 358       359 through 505       506       1042 through 1047       1062 through 1073         255       1 through 207       1 through 147       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       .       1025 through 696         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696		109 through 558	109 through 273	274 through 558	559	•	1104 through 1114
255       1 through 207       1 through 147       148 through 207       208       784 through 789       807 through 818         256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       -       1025 through 696         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696	253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
256       12 through 734       12 through 101       102 through 734       735       914 through 919       961 through 971         257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       .       1025 through 1035         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696		59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
257       378 through 518       378 through 467       468 through 518       519       607 through 612       628 through 640         258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       -       1025 through 1035         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696	255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
258       110 through 304       110 through 193       194 through 304       305       708 through 713       732 through 743         259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       .       1025 through 1035         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696	256	12 through 734	12 through 101	102 through 734	735	914 through 919	961 through 971
259       201 through 419       201 through 272       273 through 419       420       601 through 606       627 through 637         260       123 through 302       123 through 176       177 through 302       303       1279 through 1284       1301 through 1312         261       98 through 673       98 through 376       377 through 673       674       -       1025 through 1035         262       17 through 463       17 through 232       233 through 463       464       657 through 662       684 through 696	257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
260     123 through 302     123 through 176     177 through 302     303     1279 through 1284     1301 through 1312       261     98 through 673     98 through 376     377 through 673     674     -     1025 through 1035       262     17 through 463     17 through 232     233 through 463     464     657 through 662     684 through 696		110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
261     98 through 673     98 through 376     377 through 673     674     -     1025 through 1035       262     17 through 463     17 through 232     233 through 463     464     657 through 662     684 through 696				273 through 419	420	601 through 606	627 through 637
262 17 through 463 17 through 232 233 through 463 464 657 through 662 684 through 696				177 through 302	303	1279 through 1284	1301 through 1312
352 352 h.m. 1401 300 d. 1 200 300 d. 1 300 300				377 through 673	674	•	1025 through 1035
263         263 through 481         263 through 322         323 through 481         482         -         858 through 868				233 through 463	464	657 through 662	684 through 696
	263	263 through 481	263 through 322	323 through 481	482	•	858 through 868

CONT. TABLE IV

265   198 through 431   198 through 260   261 through 431   432     1064 through 266   279 through 473   279 through 362   363 through 473   474   944 through 949   970 through 1607   1020 through 268   91 through 459   91 through 330   331 through 459   460     1271 through 1607   1020 through 269   70 through 459   91 through 330   331 through 459   460     1271 through 1746   1763 through 279   12 through 487   12 through 147   148 through 327   328   1741 through 1746   1763 through 270   12 through 487   12 through 104   105 through 487   498   935 through 940   955 through 672   12 through 383   90 through 487   498   935 through 940   955 through 672   372 through 383   90 through 487   377 through 487   478 through 487   478 through 487   478 through 487   478 through 487   479 through 487   478 through 487   479 through 487	CUN	I. I ABLE IV					
278   through 473   279   through 362   363   through 473   474   944   through 949   970   through 475     268   91   through 459   91   through 320   331   through 644   645   1002   through 1007   1022   through 1027     268   970   through 459   91   through 327   328   1741   through 1746   1763   through 270   12   through 327   70   through 147   148   through 327   328   1741   through 1746   1763   through 270   12   through 327   328   335   through 940   955   through 270   12   through 383   90   through 200   201   through 487   498   335   through 940   955   through 271   301   through 487   332   through 376   377   through 487   498   335   through 487   476   through 174   738   through 487   498   335   through 487   498   335   through 487   498   335   through 487   498   335   through 480   955   through 487   498   335   through 480   955   through 487   498   336   through 480   955   through 487   498   336   through 545   530   through 545   555   through 545   542   739   through 545   555   through 545   565   throug	264	42 through 299	42 through 101	102 through 299	300	·	762 through 7,75
267   12 through 644   12 through 92   93 through 644   645   1002 through 1007   1020 through 268   91 through 459   91 through 330   331 through 459   460	265	198 through 431	198 through 260	261 through 431	432	•	1064 through 1074
268   91 through 459   91 through 330   331 through 459   460	266	279 through 473	279 through 362	363 through 473	474	944 through 949	970 through 981
269   70 through 327   70 through 147   148 through 327   328   1741 through 1746   1763 through 1740   1764 through 1740	267	12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 1031
270	268	91 through 459	91 through 330	331 through 459	460		1271 through 1281
271   90 through 383   90 through 200   201 through 383   384   609 through 614   632 through 627   332 through 541   332 through 376   377 through 541   542   739 through 744   761 through 742   739 through 744   761 through 745   745 through	269	70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
272         332 through 541         332 through 376         377 through 541         532 through 744         761 through 72           273         43 through 222         43 through 177         178 through 222         223         530 through 535         555 through 541         43 through 427         443 through 427         445 through 424         445 through 427         445 through 427         448 through 427         428         606 through 611         628 through 622         627 through 427         428         606 through 611         628 through 622         627 through 427         428         606 through 611         628 through 622         628 through 632         631 through 632         633         808 through 810         830 through 832         838 through 813         829 through 832         838 through 813         829 through 826         831 through 826         832 through 832         831 through 826         831 through 8	270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
273         43 through 222         43 through 177         178 through 222         223         530 through 535         555 through 52           274         115 through 231         115 through 180         181 through 231         232         419 through 424         445 through 42           275         232 through 384         232 through 300         301 through 384         385         650 through 655         662 through 62           276         143 through 427         143 through 286         287 through 427         428         606 through 611         628 through 62         286 through 611         628 through 62         287 through 463         464         -         762 through 62         280 through 611         830 through 301         390 through 671         672         805 through 813         829 through 826         830 through 830 through 830 through 832         831 through 834         345 through 832         331 through 832         831 t	271	90 through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
274   115 through 231   115 through 180   181 through 231   232   419 through 424   445 through 427   232 through 384   232 through 300   301 through 384   385   650 through 655   662 through 652   634 through 427   143 through 286   287 through 427   428   606 through 611   628 through 627   284 through 463   294 through 378   380 through 483   464   - 762 through 73   762 through 73   380 through 631   622 through 631   632 through 632   63 through 362   21 through 362   21 through 362   21 through 362   21 through 344   345 through 503   504   1305 through 1310   1330 through 828   21 through 503   21 through 633   64 through 201   202   637 through 642   660 through 632   63 through 632   63 through 632   64 through 201   202   637 through 642   660 through 632   63 through 632   64 through 201   202   637 through 642   660 through 632   64 through 201   202   637 through 642   660 through 643   69 through 633   69 through 1034   135 through 1034   1035   1566 through 1571   1587 through 1034   39 through 1034   1035   1566 through 1571   1587 through 1034   135 through 1034   345 through 1314   135 through 1034   135 through 1035   1566 through 1571   1587 through 285   115 through 204   205 through 285   286   505 through 510   525 through 528   115 through 344   90 through 140   141 through 344   345   500 through 505   515 through 516   527   799 through 505   515 through 516   528 through 526   161 through 328   329 through 526   527   799 through 528   161 through 322   300 through 332   333   594 through 599   613 through 629   75 through 361   212 through 361   212 through 361   362   650 through 655   673 through 629   75 through 641   50 through 576   577   737 through 742   763 through 678   154 through 576   154 through 580   361 through 576   577   737 through 742   763 through 742   763 through 679   154 through 689   361 through 589   361 through 589   49 through 491   49 through 599   49 through 491   49 through 599   49 t	272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
275   232 through 384   232 through 300   301 through 384   385   650 through 655   652 through 627   143 through 286   287 through 427   428   606 through 655   652 through 627   284 through 463   294 through 379   380 through 463   464	273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
276	274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
277         284 through 463         294 through 379         380 through 463         464         -         762 through 7           278         162 through 671         162 through 398         399 through 671         672         805 through 810         830 through 8           279         63 through 632         63 through 308         309 through 632         633         808 through 813         829 through 8           280         21 through 362         21 through 362         21 through 362         363         821 through 826         838 through 8           281         21 through 362         21 through 344         345 through 503         504         1305 through 1310         1330 through 13           282         1 through 201         1 through 63         64 through 201         202         637 through 842         660 through 62           283         39 through 1034         39 through 1034         1035         1566 through 642         660 through 62           284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through 361           285         115 through 265         115 through 264         205 through 285         286         505 through 510         525 through 51           286         90 through 344         90	275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
277         284 through 463         294 through 379         380 through 463         464         -         762 through 76           278         162 through 671         162 through 388         399 through 671         672         805 through 810         830 through 82           279         63 through 632         63 through 308         309 through 632         633         808 through 813         829 through 82           280         21 through 362         21 through 344         345 through 503         504         1305 through 1310         1330 through 132           281         21 through 503         21 through 344         345 through 503         504         1305 through 1310         1330 through 125           282         1 through 201         1 through 63         64 through 201         202         637 through 642         660 through 164           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through 167           284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through 361           285         115 through 285         115 through 284         205 through 344         345 through 311         312 through 311         57 through 311         57 through 311<	276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
278         162 through 671         162 through 398         399 through 671         672         805 through 810         830 through 82           279         63 through 632         63 through 308         309 through 632         633         808 through 813         829 through 82           280         21 through 362         21 through 362         363         821 through 826         838 through 82           281         21 through 503         21 through 344         345 through 503         504         1305 through 1310         1330 through 62           282         1 through 201         1 through 63         64 through 201         202         537 through 642         660 through 62           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 642         660 through 660           284         69 through 263         69 through 125         128 through 263         264         1173 through 171         1198 through 178         1196 through 178         1296 through 178         1296 through 181	277	284 through 463	294 through 379	380 through 463	464	1:	762 through 772
279         63 through 632         63 through 308         309 through 632         633         808 through 813         829 through 82           280         21 through 362         21 through 200         201 through 362         363         821 through 826         838 through 826           281         21 through 503         21 through 344         345 through 503         504         1305 through 1310         1330 through 632           282         1 through 201         1 through 63         64 through 201         202         637 through 642         660 through 660 through 642           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through 1571           284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through 510           285         115 through 285         115 through 285         286         505 through 510         525 through 51           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 51           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 482           289 <td< td=""><td>278</td><td>162 through 671</td><td>162 through 398</td><td>399 through 671</td><td>672</td><td>805 through 810</td><td>830 through 840</td></td<>	278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
280         21 through 362         21 through 200         201 through 362         363         821 through 826         838 through 82           281         21 through 503         21 through 344         345 through 503         504         1305 through 1310         1330 through 62           282         1 through 201         1 through 63         64 through 201         202         637 through 642         660 through 6           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through 6           284         69 through 263         69 through 263         264         1173 through 1178         1196 through 5           285         115 through 285         115 through 204         205 through 285         286         505 through 510         525 through 5           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 55         515 through 55         515 through 472         482 through 482         288         96 through 302         96 through 182         183 through 302         303         -         501 through 472         482 through 56         527         -         799 through 62         290         210 through 332         210 through 318         320 through 361	279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
281         21 through 503         21 through 344         345 through 503         504         1305 through 1310         1330 through 62           282         1 through 201         1 through 63         64 through 201         202         637 through 642         660 through 62           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through           284         69 through 263         69 through 263         264         1173 through 1178         1196 through           285         115 through 285         115 through 204         205 through 285         286         505 through 510         525 through 51           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 55           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 482           288         96 through 302         96 through 182         183 through 302         303         -         501 through 551           289         161 through 322         210 through 332         230 through 565         527         -         799 through 665           291         212 through 361         212 through 36	280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
282         1 through 201         1 through 63         64 through 201         202         637 through 642         660 through 62           283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through           284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through           285         115 through 285         115 through 204         205 through 285         286         505 through 510         525 through 52           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 52           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 482           288         96 through 302         96 through 182         183 through 302         303         -         501 through 51           289         161 through 328         329 through 526         527         -         799 through 62           290         210 through 332         210 through 299         300 through 332         333         594 through 599         613 through 62           291         212 through 361         212 through 319 </td <td>281</td> <td>21 through 503</td> <td>21 through 344</td> <td>345 through 503</td> <td>504</td> <td></td> <td>1330 through 1341</td>	281	21 through 503	21 through 344	345 through 503	504		1330 through 1341
283         39 through 1034         39 through 134         135 through 1034         1035         1566 through 1571         1587 through 284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through 528         1196 through 285         115 through 285         115 through 285         286         505 through 510         525 through 52         286         505 through 510         525 through 52         586 through 526         505 through 510         525 through 52         570 through 311         312         467 through 472         482 through 42         482 through 43         482 through 432         483 through 311         312         467 through 472         482 through 42         482 through 42         483 through 472         482 through 482 through 482         483 through 472         482 through 482 through 482         591 through 472         482 through 482 through 482         591 through 482         329 through 596         527         -         799 through 597 through 599 through 599         613 through 66         631 through 66         650 through 599         613 through 66         631 through 66         632 through 655 through 655 through 673 through 66         631 through 66         632 through 677 through 782         801 through 66         631 through 67         632 through 677 through 782         801 through 678 through 678         773 through 782         801 through 678 through 678 <td>282</td> <td>1 through 201</td> <td>1 through 63</td> <td>64 through 201</td> <td>202</td> <td></td> <td></td>	282	1 through 201	1 through 63	64 through 201	202		
284         69 through 263         69 through 125         126 through 263         264         1173 through 1178         1196 through 285           285         115 through 285         115 through 204         205 through 285         286         505 through 510         525 through 52           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 52           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 48           288         96 through 302         96 through 182         183 through 302         303         -         501 through 51           289         161 through 526         161 through 328         329 through 526         527         -         799 through 63           290         210 through 332         210 through 299         300 through 332         333         594 through 599         613 through 62           291         212 through 361         212 through 319         320 through 361         362         650 through 655         673 through 62           292         75 through 482         75 through 31         320 through 482         483         595 through 600         618 through 62           293         50 through 6	283	39 through 1034	39 through 134	135 through 1034	1035	·	1587 through 1597
285         115 through 285         115 through 204         205 through 285         286         505 through 510         525 through 52           286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 52           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 48           288         96 through 302         96 through 182         183 through 302         303         -         501 through 59           289         161 through 526         161 through 328         329 through 526         527         -         799 through 81           290         210 through 332         210 through 299         300 through 332         333         594 through 599         613 through 62           291         212 through 361         212 through 361         362         650 through 655         673 through 62           292         75 through 482         75 through 482         483         595 through 600         618 through 62           293         50 through 631         50 through 244         245 through 631         632         777 through 782         801 through 81           294         154 through 576         154 through 360         361 through 897	284	69 through 263	69 through 125	126 through 263	264		1196 through 1205
286         90 through 344         90 through 140         141 through 344         345         500 through 505         515 through 52           287         57 through 311         57 through 107         108 through 311         312         467 through 472         482 through 48           288         96 through 302         96 through 182         183 through 302         303         -         501 through 51           289         161 through 526         161 through 328         329 through 526         527         -         799 through 81           290         210 through 332         210 through 299         300 through 332         333         594 through 599         613 through 62           291         212 through 361         212 through 319         320 through 361         362         650 through 655         673 through 62           292         75 through 482         75 through 128         129 through 482         483         595 through 600         618 through 62           293         50 through 631         50 through 244         245 through 631         632         777 through 742         763 through 81           294         154 through 897         154 through 360         361 through 897         898         1017 through 1022         1044 through 74         1044 through 74         295 <t< td=""><td>285</td><td>115 through 285</td><td>115 through 204</td><td>205 through 285</td><td>286</td><td></td><td><del> </del></td></t<>	285	115 through 285	115 through 204	205 through 285	286		<del> </del>
287       57 through 311       57 through 107       108 through 311       312       467 through 472       482 through 49         288       96 through 302       96 through 182       183 through 302       303       501 through 50         289       161 through 526       161 through 328       329 through 526       527       799 through 81         290       210 through 332       210 through 299       300 through 332       333       594 through 599       613 through 62         291       212 through 361       212 through 319       320 through 361       362       650 through 655       673 through 62         292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 14         296       146 through 383       126 through 253       254 through 383       384       726 through 731       743 through 74	286	90 through 344	90 through 140	141 through 344	345		515 through 527
288       96 through 302       96 through 182       183 through 302       303       .       501 through 52         289       161 through 526       161 through 328       329 through 526       527       .       799 through 81         290       210 through 332       210 through 299       300 through 332       333       594 through 599       613 through 62         291       212 through 361       212 through 319       320 through 361       362       650 through 655       673 through 62         292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 144 through 102         296       146 through 292       146 through 253       254 through 383       384       726 through 731       743 through 74         298       66 through 497       66 through 239       240 through 497       498       594 t	287	57 through 311	57 through 107	108 through 311	312		482 through 493
289       161 through 526       161 through 328       329 through 526       527       799 through 81         290       210 through 332       210 through 299       300 through 332       333       594 through 599       613 through 62         291       212 through 361       212 through 319       320 through 361       362       650 through 655       673 through 68         292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 897       598       1017 through 742       763 through 77         295       154 through 897       154 through 253       254 through 897       898       1017 through 1022       1044 through 44         296       146 through 292       146 through 253       254 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 239       240 through 497       498       594 through 737       750 through 76         299       49 through 411       49 through 96       97 through 534       535       593 through 598	288	96 through 302	96 through 182	183 through 302	303	<del> </del>	501 through 514
290       210 through 332       210 through 299       300 through 332       333       594 through 599       613 through 62         291       212 through 361       212 through 319       320 through 361       362       650 through 655       673 through 68         292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 1         296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 62         298       66 through 497       66 through 497       498       594 through 737       750 through 76         300       49 through 534       49 through 96       97 through 534       535       593 through 598	289	161 through 526	161 through 328	329 through 526	527	† <del>.                                    </del>	
291       212 through 361       212 through 319       320 through 361       362       650 through 655       673 through 682         292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 1         296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545	290	210 through 332	210 through 299	300 through 332	333	594 through 599	613 through 625
292       75 through 482       75 through 128       129 through 482       483       595 through 600       618 through 62         293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 897       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 1         296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 239       240 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545       560 through 57         302       56 through 268       56 through 189       181 through 360       181 through 415<	291	212 through 361	212 through 319	320 through 361	362	650 through 655	673 through 684
293       50 through 631       50 through 244       245 through 631       632       777 through 782       801 through 81         294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 1         296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 411       412       732 through 737       750 through 62         300       49 through 534       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545       560 through 57	.292	75 through 482	75 through 128	129 through 482	483	595 through 600	
294       154 through 576       154 through 360       361 through 576       577       737 through 742       763 through 77         295       154 through 897       154 through 360       361 through 897       898       1017 through 1022       1044 through 1         296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 239       240 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 411       412       732 through 737       750 through 62         300       49 through 534       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545       560 through 57	293	50 through 631	50 through 244	245 through 631	632	·	<del></del>
295     154 through 897     154 through 360     361 through 897     898     1017 through 1022     1044 through 1       296     146 through 292     146 through 253     254 through 292     293     395 through 400     433 through 44       297     126 through 383     126 through 167     168 through 383     384     726 through 731     743 through 75       298     66 through 497     66 through 239     240 through 497     498     594 through 599     618 through 62       299     49 through 411     49 through 96     97 through 411     412     732 through 737     750 through 76       300     49 through 534     49 through 96     97 through 534     535     593 through 598     612 through 62       301     86 through 415     86 through 145     146 through 415     416     540 through 545     560 through 57       302     56 through 268     56 through 180     181 through 268     560 through 57	294	154 through 576	154 through 360	361 through 576	577	737 through 742	
296       146 through 292       146 through 253       254 through 292       293       395 through 400       433 through 44         297       126 through 383       126 through 167       168 through 383       384       726 through 731       743 through 75         298       66 through 497       66 through 239       240 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 411       412       732 through 737       750 through 76         300       49 through 534       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545       560 through 57         302       56 through 268       56 through 100       101 through 268       560 through 57	295	154 through 897	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
297       126 through 383       126 through 167       168 through 383 .       384       726 through 731       743 through 75         298       66 through 497       66 through 239       240 through 497       498       594 through 599       618 through 62         299       49 through 411       49 through 96       97 through 411       412       732 through 737       750 through 76         300       49 through 534       49 through 96       97 through 534       535       593 through 598       612 through 62         301       86 through 415       86 through 145       146 through 415       416       540 through 545       560 through 57         302       56 through 268       56 through 180       101 through 369       202       500 through 57	296	146 through 292	146 through 253	254 through 292	293	395 through 400	433 through 444
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- I would be a second of the s	302	56 through 268	56 through 100	101 through 268			
303   27 through 229   22 through 100   100   100	303	32 through 328	32 through 103	104 through 328			528 through 539
304 21 through 527 21 through 95 05 through 527 700	304	21 through 527	21 through 95	96 through 527			953 through 963
305 147 through 647 147 through 274 275 through 647 049	305	147 through 647	147 through 374	375 through 647			668 through 681

CONT. TABLE IV

262 through 371   262 through 372   373 through 374   472   683 through 683   682 through 1632     307   74 through 1216   74 through 1726   173 through 1216   127 through 1832   1864 through 1852     308   48 through 614   48 through 39   90 through 184   185   482 through 487   505 through 517     309   185 through 334   185 through 272   273 through 347   348   1037 through 1042   1071 through 1082     310   195 through 347   195 through 179   180 through 347   348   1037 through 1042   1071 through 1082     311   90 through 815   90 through 179   180 through 1815   816   833 through 888   995 through 981     312   52 through 348   272 through 348   335 through 558   572 through 683     313   172 through 348   172 through 354   355 through 348   439   682 through 687   685 through 687     314   148 through 360   148 through 276   277 through 360   367   770 through 775   792 through 893     315   191 through 336   175 through 276   277 through 360   367   770 through 775   792 through 893     316   191 through 553   191 through 276   277 through 563   554   766 through 771   804 through 817     317   108 through 603   106 through 216   277 through 560   567   1583 through 1588   1614 through 167     318   47 through 560   47 through 216   271 through 560   567   1583 through 1588   1614 through 162     319   99 through 427   99 through 129   281 through 581   582   1006 through 1588   1614 through 162     320   44 through 141   44 through 142   113 through 814   815   282   1006 through 1688     321   37 through 564   47 through 159   191 through 407   408   1008 through 504   516 through 589     322   27 through 427   107 through 182   282 through 327   333   34 through 169   34 through 182   34 through 182   34 through 182   34 through 183   34 through 184   34 through 185   352   333   34 through 186   34 through 187   38 through 187	COV	IT. TABLE IV					•
308	306	262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
185 through 334   185 through 295   286 through 334   335   355 through 336   332 through 405   331   195 through 347   195 through 272   273 through 815   816   883 through 888   905 through 1082   311   90 through 815   90 through 179   180 through 815   816   883 through 888   905 through 916   312   52 through 331   32 through 331   32 through 331   32 through 331   32 through 332   32 through 333   375 through 438   393   882 through 886   865 through 693   313   172 through 438   375 through 438   377 through 526   226 through 326   367   770 through 775   792 through 803   315   175 through 336   175 through 276   227 through 336   337   - 812 through 823   316   191 through 338   175 through 276   277 through 336   337   - 812 through 823   316   191 through 304   305 through 553   554   766 through 771   804 through 817   317   106 through 603   106 through 126   217 through 603   604   - 1102 through 1112   318   47 through 124   125 through 566   887   1593 through 1586   1614 through 123   319   99 through 371   99 through 290   291 through 311   322   33 through 581   3 through 182   183 through 581   582   - 1006 through 496   513 through 674   320   44 through 831   3 through 182   183 through 581   582   - 1006 through 1016   322   107 through 193   191 through 332   291 through 332   301 through 831   3 through 83   84 through 407   408   1008 through 1013   1032 through 1016   322   107 through 497   45 through 498   41 through 496   13 through 332   301 through 332   301 through 332   301 through 332   301 through 333   301 through 334   301 through 337   301 through 340   301 through 340   301 through 340   301 through 340   301 through 341   301 through 341   301 through 341   301 through 342   301 through 341   301 through 341	307	74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
195 through 347   195 through 272   273 through 347   348   1037 through 1042   1071 through 1082   311   30 through 815   30 through 179   180 through 815   816   883 through 888   905 through 916   312   52 through 513   52 through 524   325 through 513   52 through 525   355 through 438   439   682 through 687   685 through 697   314   148 through 366   148 through 255   225 through 366   367   770 through 775   792 through 823   315   175 through 338   175 through 376   277 through 336   337   812 through 687   812 through 823   316   191 through 553   191 through 340   305 through 553   554   766 through 775   792 through 823   316   191 through 553   191 through 340   305 through 553   554   766 through 775   792 through 823   318   47 through 556   47 through 276   277 through 556   587   1583 through 1588   1614 through 1623   319   99 through 566   47 through 124   125 through 566   587   1583 through 1588   1614 through 1623   319   99 through 371   39 through 182   133 through 814   815   978 through 823   310 through 818   31 through 182   133 through 814   815   978 through 829   321 through 814   44 through 112   113 through 814   815   978 through 829   321 through 815   31 through 816   31 through 817   322   107 through 427   107 through 182   133 through 814   45 through 829   321 through 322   201 through 251   252 through 332   333   888 through 103   302 through 1042   324   201 through 324   201 through 251   252 through 332   333   888 through 486   388 through 486   388 through 487   330 through 389   331 through 343   331 through 343   331 through 486   467 through 486   467 through 486   467 through 486   467 through 487   331 through 389   331 through 340   331 through 340   331 through 341   331 through 341   331 through 343   331 through 343   331 through 343   331 through 344   331 through 345   348 through 346   348 through 355   348 through 356   357 through 357   357 through 358   358 through 359   341 through 340   341 through 346   341 through 346   341 through 346   341 thr	308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
311   90 through 815   90 through 717   180 through 815   816   883 through 888   905 through 916   312   52 through 513   52 through 513   52 through 523   325 through 523   325 through 523   325 through 438   439   682 through 687   685 through 687   325 through 823   337   770 through 775   792 through 823   315   775 through 526   326 through 326   327   770 through 775   792 through 823   316   191 through 523   191 through 304   305 through 553   554   766 through 771   326 through 827   317   106 through 683   191 through 304   305 through 553   554   766 through 771   326 through 827   318   47 through 683   106 through 216   217 through 586   587   1583 through 1588   1614 through 1623   319   99 through 371   99 through 390   291 through 371   372   491 through 496   513 through 689   321   3 through 581   3 through 122   183 through 581   3 through 487   107 through 190   191 through 487   428   499 through 504   516 through 523   32 through 427   107 through 190   191 through 427   428   499 through 504   516 through 523   325 through 437   327 through 586   326 through 427   408   1008 through 1013   1032 through 1016   322   201 through 332   201 through 255   256 through 523   333   -	309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
Section   Sect	310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
172 through 438   172 through 354   355 through 438   439   682 through 687   685 through 697   314   148 through 366   148 through 225   226 through 366   367   770 through 775   792 through 803   315   175 through 336   175 through 276   277 through 336   337   812 through 873   315   175 through 336   315 through 573   319 through 583   319 through 583   319 through 583   319 through 216   217 through 585   554   786 through 771   804 through 817   318   47 through 585   47 through 216   217 through 586   587   1583 through 1588   1614 through 1623   318   39 through 371   99 through 220   291 through 371   372   491 through 498   513 through 582   320   44 through 1812   113 through 371   372   491 through 498   513 through 582   320   44 through 182   183 through 581   582   - 1006 through 583   320   44 through 182   183 through 581   582   - 1006 through 583   321 through 182   183 through 581   3 through 389   324   207 through 427   107 through 189   191 through 427   428   489 through 504   516 through 529   323   45 through 427   107 through 251   252 through 332   333   - 89 through 332   201 through 251   252 through 332   333   - 89 through 880   322   217 through 581   217 through 251   256 through 543   544   - 1206 through 1913   1032 through 1914   328   217 through 584   291 through 181   119 through 446   447   330 through 393   348 through 480   328 through 446   18 through 140   141 through 446   447   330 through 393   331 through 381   348 through 446   447   330 through 393   331 through 384   331 through 387   388 through 432   331 through 387   388 through 393   311 through 384   381 through 387   388 through 391   332 through 391   334 through 387   388 through 488   336 through 391   331 through 384   391 through 385   391 through 38	311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
148   148   148   149   148   149	312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
315   175 through 336   175 through 276   277 through 336   337     812 through 823   316   191 through 553   191 through 304   305 through 553   554   766 through 771   804 through 817   317   106 through 603   106 through 216   217 through 603   604     1102 through 1112   318   47 through 586   47 through 124   125 through 586   587   1583 through 1588   1614 through 1623   319   99 through 371   99 through 290   291 through 371   372   491 through 496   513 through 524   320   44 through 114   44 through 112   113 through 814   815     978 through 889   321   3 through 427   107 through 190   191 through 427   428   499 through 504   516 through 504   322   107 through 427   107 through 190   191 through 427   428   449 through 504   516 through 504   323   45 through 427   45 through 821   252 through 427   428   449 through 504   516 through 607   323   45 through 437   201 through 251   252 through 332   333     869 through 1013   322 through 1042   324   201 through 322   201 through 255   256 through 543   544     1206 through 1217   326   18 through 446   18 through 140   141 through 446   447   930 through 935   948 through 959   327   29 through 724   29 through 181   119 through 566   587   1304 through 1309   1334 through 1944   329   331 through 337   338 through 337   338 through 343   331 through 343   338 through 342   433   548 through 553   573 through 585   330   59 through 703   59 through 387   388 through 371   372   373 through 373   374 through 374   375 through 374   375 through 172   328 through 375   376 through 377   372 through 378   373 through 181   372 through 182   331 through 384   386 through 381   376 through 384   386 through 384   386 through 387   381 through 384   386 through 384   386 through 384   386 through 387   391 through 387   391 through 387   3	313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
191 through 553   191 through 304   305 through 553   554   766 through 771   804 through 817   317   106 through 603   106 through 216   217 through 603   604	314	148.through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
106 through 603   106 through 216   217 through 603   604     1102 through 1112	315	175 through 336	175 through 276	277 through 336	337		812 through 823
318	316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
319   99 through 371   99 through 290   291 through 371   372   481 through 496   513 through 524   320   44 through 814   44 through 112   113 through 814   815	317	106 through 603	106 through 216	217 through 603	604		1102 through 1112
320	318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
321   3 through 581   3 through 182   183 through 581   582     1006 through 1016	319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
322   107 through 427   107 through 190   191 through 427   428   499 through 504   516 through 529   323   45 through 407   45 through 83   84 through 407   408   1008 through 1013   1032 through 1042   324   201 through 332   201 through 251   252 through 332   333   -	320	44 through 814	44 through 112	113 through 814	815		978 through 989
323   45 through 407   45 through 83   84 through 407   408   1008 through 1013   1032 through 1042	321	3 through 581	3 through 182	183 through 581	582	<del> </del>	1006 through 1016
324         201 through 332         201 through 251         252 through 332         333         869 through 880           325         217 through 543         217 through 255         256 through 332         333         -         1206 through 1217           326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 240         128 through 232         233         617 through 337         351 through 363           334         91 through 249 <td>322</td> <td>107 through 427</td> <td>107 through 190</td> <td>191 through 427</td> <td>428</td> <td>499 through 504</td> <td>516 through 529</td>	322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
325         217 through 543         217 through 255         256 through 543         544         .         1206 through 1217           326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         386 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 585           330         59 through 752         672 through 722         723 through 752         753         .         1150 through 914           331         672 through 752         672 through 722         723 through 752         753         .         1150 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 240         241 through 384         385         461 through 372         389 through 496           336         54 through 59	323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         -         1150 through 914           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 291         292         367 through 372         389 through 496           336         54 through 384         196 through 227	324	201 through 332	201 through 251	252 through 332	333		869 through 880
327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 722         723 through 752         753         -         1150 through 914           331         672 through 752         672 through 722         723 through 311         312         332 through 337         351 through 363           333         80 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 466           336         54 through 846	325	217 through 543	217 through 255	256 through 543	544	-	1206 through 1217
328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 722         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         -         1150 through 1161           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 281         91 through 249         220 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 496           336         54 through 866         133 through 345         346 through 866         847         -         890 through 965           337 <td< td=""><td>326</td><td>18 through 446</td><td>18 through 140</td><td>141 through 446</td><td>447</td><td>930 through 935</td><td>948 through 959</td></td<>	326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
329 331 through 432 331 through 387 388 through 432 433 548 through 553 573 through 585 330 59 through 703 59 through 220 221 through 703 704 886 through 891 903 through 914 331 672 through 752 672 through 722 723 through 752 753	327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         .         1150 through 1161           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 496           336         54 through 590         54 through 345         346 through 846         847         .         890 through 901           338         138 through 671         138 through 345         346 through 846         847         .         890 through 901           339         124 through 411         124 through 186         187 through 671         672         1319 through 1324         1338 through 372           340         372 through 494         372 through 443	328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
331       672 through 752       672 through 722       723 through 752       753	329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
332       57 through 311       57 through 128       129 through 311       312       332 through 337       351 through 363         333       80 through 232       80 through 127       128 through 232       233       617 through 622       634 through 645         334       91 through 291       91 through 219       220 through 291       292       367 through 372       389 through 400         335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 345       346 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106	330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
333 80 through 232 80 through 127 128 through 232 233 617 through 622 634 through 645 334 91 through 291 91 through 219 220 through 291 292 367 through 372 389 through 400 335 196 through 384 196 through 240 241 through 384 385 461 through 466 485 through 496 336 54 through 590 54 through 227 228 through 590 591 . 955 through 965 337 133 through 846 133 through 345 346 through 846 847 . 890 through 901 338 138 through 671 138 through 248 249 through 671 672 1319 through 1324 1338 through 1347 339 124 through 411 124 through 186 187 through 411 412 948 through 953 971 through 983 340 372 through 494 372 through 443 444 through 494 495 708 through 713 732 through 745 341 112 through 450 112 through 192 193 through 450 451 1053 through 1058 1095 through 1106 342 117 through 866 117 through 170 171 through 866 867 1159 through 1164 1178 through 1190 343 13 through 485 13 through 75 76 through 465 466 1035 through 1040 1060 through 1070 344 2 through 718 2 through 76 77 through 718 719 1170 through 1175 1203 through 1213 345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	331	672 through 752	672 through 722	723 through 752	753	-	1150 through 1161
334         91 through 291         91 through 219         220 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 496           336         54 through 590         54 through 227         228 through 590         591         .         955 through 965           337         133 through 846         133 through 345         346 through 846         847         .         890 through 901           338         138 through 671         138 through 248         249 through 671         672         1319 through 1324         1338 through 1347           339         124 through 411         124 through 186         187 through 411         412         948 through 953         971 through 983           340         372 through 494         372 through 443         444 through 494         495         708 through 713         732 through 745           341         112 through 450         112 through 192         193 through 450         451         1053 through 1058         1095 through 1106           342         117 through 866         117 through 71         171 through 866         867         1159 through 1164         1178 through 1190           343	332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 866       867       1159 through 1164       1178 through 1190         343       13 through 718       2 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 709       710       943 through 948       963 through 973	333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
336         54 through 590         54 through 227         228 through 590         591         -         955 through 965           337         133 through 846         133 through 345         346 through 846         847         -         890 through 901           338         138 through 671         138 through 248         249 through 671         672         1319 through 1324         1338 through 1347           339         124 through 411         124 through 186         187 through 411         412         948 through 953         971 through 983           340         372 through 494         372 through 443         444 through 494         495         708 through 713         732 through 745           341         112 through 450         112 through 192         193 through 450         451         1053 through 1058         1095 through 1106           342         117 through 866         117 through 866         867         1159 through 1164         1178 through 1190           343         13 through 75         76 through 465         466         1035 through 1040         1060 through 1070           344         2 through 718         2 through 76         77 through 718         719         1170 through 1175         1203 through 973           345         86 through 709         86 through 709	334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 921         345       86 through 320       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321<	335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	336	54 through 590	54 through 227	228 through 590	591		955 through 965
339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	337	133 through 846	133 through 345	346 through 846	847		890 through 901
340 372 through 494 372 through 443 444 through 494 495 708 through 713 732 through 745 341 112 through 450 112 through 192 193 through 450 451 1053 through 1058 1095 through 1106 342 117 through 866 117 through 170 171 through 866 867 1159 through 1164 1178 through 1190 343 13 through 465 13 through 75 76 through 465 466 1035 through 1040 1060 through 1070 344 2 through 718 2 through 76 77 through 718 719 1170 through 1175 1203 through 1213 345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
343 13 through 465 13 through 75 76 through 465 466 1035 through 1040 1060 through 1070 344 2 through 718 2 through 76 77 through 718 719 1170 through 1175 1203 through 1213 345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
344     2 through 718     2 through 76     77 through 718     719     1170 through 1175     1203 through 1213       345     86 through 709     86 through 361     362 through 709     710     943 through 948     963 through 973       346     63 through 320     63 through 179     180 through 320     321     771 through 776     799 through 810	342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
247 200 days 4.10 200 days 200 200 200 200 200 200 200 200 200 20	345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
347 299 through 418 299 through 379 380 through 418 419 739 through 744 762 through 771	346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
	347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771

CONT. TABLE IV

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348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340		1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326		718 through 729
355	78 through 731	78 through 227	228 through 731	732	1.	1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949		<del></del>
360	69 through 434	69 through 236	237 through 434	435	419 through 424	1016 through 1028
361	628 through 804	628 through 711	712 through 804	805		441 through 452
362	70 through 366	70 through 108	109 through 366	367	496 through 501	864 through 875
363	70 through 366	70 through 108	109 through 366	367		521 through 531
364	111 through 434	111 through 185	186 through 434	435		1233 through 1244
365	19 through 567	19 through 63	64 through 567	568	749 through 754	618 through 631
366	19 through 312	19 through 63	64 through 312	313		771 through 781
367	64 through 612	64 through 234	235 through 612	613	896 through 901	921 through 931
368	39 through 458	39 through 80	81 through 458	459		839 through 849
369	9 through 185	9 through 50	51 through 185	ļ <u>.</u>	613 through 618	633 through 644
370	14 through 316	14 through 121	122 through 316	186	440.1	906 through 918
371	70 through 1092	70 through 234	235 through 1092	317	442 through 447	458 through 471
372	274 through 597	274 through 399	400 through 597	1093	1475 through 1480	1493 through 1504
373	230 through 469	230 through 307	308 through 469	598	731 through 736	754 through 765
374	72 through 545	72 through 203		470	1004 through 1009	1027 through 1040
375	36 through 425	36 through 119	204 through 545	546	•	1151 through 1162
376	155 through 751	155 through 340	120 through 425	426	1215 through 1220	1240 through 1250
377	46 through 585	46 through 120	341 through 751	752	912 through 917	937 through 947
		40 anuagn 120	121 through 585	586	584 through 589	606 through 619

TABLE V

		I ABLE V	
lđ	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55	•	1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180		1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7	•	1 through 7
152	-42 through 157	-42 through -1	1 through 157
153	1 through 43		1 through 43
154	-37 through 13	-37 through -1	1 through 13
155	1 through 153	•	1 through 153
156	1 through 67	•	1 through 67
157	1 through 87	•	1 through 87
158	-85 through 165	-85 through -1	1 through 165
159	1 through 24		1 through 24
160	1 through 228		1 through 228
161	-20 through 66	-20 through -1	1 through 66
162	1 through 44	•	1 through 44
163	-58 through 256	-58 through -1	1 through 256
164	-80 through 9	-80 through -1	1 through 9
165	-15 through 83	-15 through -1	1 through 83
166	-36 through 56	-36 through -1	1 through 56
167	-16 through 335	-16 through -1	1 through 335
168	-47 through 91	-47 through -1	1 through 91
169	-73 through 28	-73 through -1	1 through 28
170	-68 through 184	-68 through -1	1 through 184
171	-68 through 282	-68 through -1	1 through 282
172	-68 through 322	-68 through -1	1 through 322
173	-82 through 108	-82 through -1	1 through 108
174	-232 through 53	-232 through -1	1 through 53
175	1 through 153		1 through 153
176	1 through 49	-	1 through 49
177	-24 through 75	-24 through -1	1 through 75
178	-37 through 58	-37 through -1	1 through 58
179	-23 through 98	-23 through -1	1 through 98
180	1 through 59		1 through 59
181	-14 through 72	-14 through -1	1 through 72
182	-58 through 107	-58 through -1	1 through 107
183	-35 through 45	-35 through -1	1 through 45
184	-21 through 52	-21 through -1	1 through 52
185	1 through 98		1 through 98
186	-21 through 91	-21 through -1	1 through 91
187	-44 through 26	-44 through -1	1 through 26
188	-13 through 79	-13 through -1	1 through 79
189	-42 through 165	-42 through -1	1 through 165
190	1 through 201		1 through 201

CONT. TABLE V

CUNT. TABLE V			
191	-37 through 342	-37 through -1	1 through 342
192	1 through 112	•	1 through 112
193	1 through 43	•	1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30		1 through 30
198	-48 through 64	-48 through -1	1 through 64
199	1 through 54		1 through 54
200	-21 through 130	-21 through -1	1 through 130
201	-25 through 203	-25 through -1	1 through 203
202	-47 through 17	-47 through -1	1 through 17
203	-31 through 115	-31 through -1	1 through 115
204	1 through 87		1 through 87
205	-27 through 13	-27 through -1	1 through 13
206	1 through 154	·	
207	1 through 101		1 through 154
208	-22 through 434	-22 through -1	1 through 101
209	-17 through 81	-17 through -1	1 through 434
210	-29 through 54	-29 through -1	1 through 81
211	-23 through 206	-23 through -1	1 through 54
212	-21 through 131	-23 through -1	1 through 206
213	-54 through 125	-54 through -1	1 through 131
214	-92 through 177	-92 through -1	1 through 125
215	-22 through 113	-32 through -1	1 through 177
216	-38 through 29		1 through 113
217	-54 through 71	-38 through -1 -54 through -1	1 through 29
218	-21 through 355	-21 through -1	1 through 71
219	-30 through 181	-30 through -1	1 through 355
220	-60 through 94		1 through 181
221	-42 through 81	-60 through -1	1 through 94
222	-19 through 327	-42 through -1	1 through 81
223	-20 through 190	-19 through -1	1 through 327
224	-20 through 164	-20 through -1	1 through 190
225	-22 through 205	-20 through -1 -22 through -1	1 through 164
226	-41 through 33	-41 through -1	1 through 205
227	1 through 73	-41 through -1	1 through 33
228	-16 through 66	16 Abraugh 1	1 through 73
229	-56 through 63	-16 through -1	1 through 66
230	1 through 54	-56 through -1	1 through 63
231	-14 through 196	14.4	1 through 54
232	1 through 108	-14 through -1	1 through 196
233	-18 through 25	10 ab	1 through 108
234	1 through 36	-18 through -1	1 through 25
235	-13 through 294	100	1 through 36
236	-32 through 74	-13 through -1	1 through 294
237	-19 through 23	-32 through -1	1 through 74
238	-20 through 97	-19 through -1	1 through 23
239	-20 through 97	-20 through -1	1 through 97
240		-37 through -1	1 through 141
241	-27 through 99	-27 through -1	1 through 99
378	-115 through 59	-115 through -1	1 through 59
379	-20 through 32	-20 through -1	1 through 32
380	-23 through 170	-23 through -1	1 through 170
500	-14 through 68	-14 through -1	1 through 68

CONT. TABLE V

ONT. TABLE V			•
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	· 1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	1 through 66
401	-21 through 57	·21 through ·1	1 through 57
402	-28 through 37	-28 through -1	1 through 37
403	-27 through 184	-27 through -1	1 through 184
404	-80 through 43	-80 through -1	1 through 43
405	-26 through 60	-26 through -1	1 through 60
406	-31 through 131	-31 through -1	1 through 131
407	-37 through 61	-37 through -1	1 through 61
408	-15 through 55	-15 through -1	1 through 55
409	-45 through 15	-45 through -1	1 through 15
410	-22 through 17	-22 through -1	1 through 17
411	-23 through 28	-23 through -1	1 through 28
412	-48 through 47	-48 through -1	1 through 47
413	-32 through 28	-32 through -1	1 through 28
414	-79 through 91	-79 through -1	1 through 91
415	-82 through 108	-82 through -1	1 through 108
416	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
418	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	
422	-30 through 27	-30 through -1	1 through 46
423	-17 through 68	-17 through -1	1 through 27
424	-17 through 68	-17 through -1	1 through 68
425	-29 through 40	-29 through -1	1 through 68
426	-56 through 66	-56 through -1	1 through 40
427	-30 through 11	-30 through -1	1 through 66
428	-36 through 14	-36 through -1	1 through 11
429	-18 through 118	-18 through -1	1 through 14
430	-65 through 129		1 through 118
431	-69 through 72	-65 through -1	1 through 129
432	-69 through 179	-69 through -1	1 through 72
433	-36 through 13	-69 through -1	1 through 179
434	-14 through 72	-36 through -1	1 through 13
434	-14 through 72 -58 through 86	-14 through -1	1 through 72
700	.ao minafii oo	-58 through -1	1 through 86

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CONT. TABLE	V		
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	-76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	-26 through -1	1 through 25
448	-30 through 212	-30 through -1	1 through 212
449	-60 through 94	-60 through -1	1 through 94
450	-61 through 28	-61 through -1	1 through 28
451	-26 through 47	-26 through -1	1 through 47
452	-34 through 20	-34 through -1	1 through 20
453	-38 through 83	-38 through -1	1 through 83
454	-37 through 129	-37 through -1	1 through 129
455	-26 through 154	-26 through -1	1 through 154
456	-64 through 27	-64 through -1	1 through 27
457	-23 through 234	-23 through -1	1 through 234
458	-60 through 133	-60 through -1	1 through 133
459	-28 through 79	-28 through -1	1 through 79
460	-13 through 108	-13 through -1	1 through 108
461	-17 through 27	-17 through -1	1 through 27
462	-13 through 96	-13 through -1	1 through 96
463	41 through 102	-41 through -1	1 through 102
464	-30 through 202	-30 through -1	1 through 202
465	-21 through 40	-21 through -1	1 through 40
466	-19 through 15	-19 through -1	1 through 15
467	-54 through 161	-54 through -1	1 through 161
468	-17 through 10	-17 through -1	1 through 10
469	-24 through 61	-24 through -1	1 through 61
470	-16 through 35	-16 through -1	1 through 35
471	-43 through 24	-43 through -1	1 through 24
472	-15 through 48	-15 through -1	1 through 48
473	-58 through 121	-58 through -1	1 through 121
474	-71 through 167	-71 through -1	1 through 167
475	-37 through 141	-37 through -1	1 through 141
476	-21 through 75	-21 through -1	1 through 75
477	-24 through 17	-24 through -1	1 through 17
478	-27 through 86	-27 through -1	1 through 86
479	-18 through 232	-18 through -1	1 through 232
480	-21 through 130	-21 through -1	1 through 130
481	-25 through 214	-25 through -1	1 through 214
482	-92 through 116	-92 through -1	1 through 116
483	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
485	-16 through 49	-16 through -1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15

491         47 through 17         47 through -1         1 through 17           492         -50 through 168         -50 through -1         1 through 168           493         -15 through 201         -15 through -1         1 through 201           494         -19 through 115         -19 through -1         1 through 115           495         -16 through 69         -16 through -1         1 through 69           496         -29 through 263         -29 through -1         1 through 263           497         -56 through 66         -56 through -1         1 through 66           498         -28 through 31         -28 through -1         1 through 31           499         -13 through 86         -13 through -1         1 through 86           500         -13 through 86         -13 through -1         1 through 86           501         -25 through 83         -25 through -1         1 through 83           502         -15 through 168         -15 through -1         1 through 168           503         -15 through 126         -57 through -1         1 through 168           504         -57 through 126         -57 through -1         1 through 126           505         -14 through 126         -14 through -1         1 through 126 <td< th=""><th></th><th></th><th></th><th></th></td<>				
491       -47 through 17       -47 through -1       1 through 17         492       -50 through 168       -50 through -1       1 through 168         493       -15 through 201       -15 through -1       1 through 201         494       -19 through 115       -19 through -1       1 through 115         495       -16 through 69       -16 through -1       1 through 69         496       -29 through 263       -29 through -1       1 through 69         497       -56 through 66       -56 through -1       1 through 263         498       -28 through 31       -28 through -1       1 through 31         499       -13 through 86       -13 through -1       1 through 86         500       -13 through 86       -13 through -1       1 through 86         501       -25 through 83       -25 through -1       1 through 83         502       -15 through 168       -15 through -1       1 through 83         503       -15 through 126       -57 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 45       -14 through -1       1 through 45         506       -14 through 45       -14 through -1       1 through 65 <t< td=""><td>490</td><td>-52 through 111</td><td>-52 through -1</td><td>1 through 111</td></t<>	490	-52 through 111	-52 through -1	1 through 111
492       -50 through 168       -50 through -1       1 through 168         493       -15 through 201       -15 through -1       1 through 201         494       -19 through 115       -19 through -1       1 through 115         495       -16 through 69       -16 through -1       1 through 69         496       -29 through 263       -29 through -1       1 through 263         497       -56 through 66       -56 through -1       1 through 263         498       -28 through 31       -28 through -1       1 through 31         499       -13 through 86       -13 through -1       1 through 86         500       -13 through 86       -13 through -1       1 through 86         501       -25 through 83       -25 through -1       1 through 86         502       -15 through 168       -15 through -1       1 through 168         503       -15 through 83       -15 through -1       1 through 168         504       -57 through 126       -57 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 45       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 65		-47 through 17		
493         -15 through 201         -15 through -1         1 through 201           494         -19 through 115         -19 through -1         1 through 115           495         -16 through 69         -16 through -1         1 through 69           496         -29 through 263         -29 through -1         1 through 263           497         -56 through 66         -56 through -1         1 through 66           498         -28 through 31         -28 through -1         1 through 31           499         -13 through 86         -13 through -1         1 through 86           500         -13 through 86         -13 through -1         1 through 86           501         -25 through 83         -25 through -1         1 through 83           502         -15 through 168         -15 through -1         1 through 168           503         -15 through 83         -15 through -1         1 through 83           504         -57 through 126         -57 through -1         1 through 83           505         -14 through 126         -14 through -1         1 through 126           506         -14 through 45         -14 through -1         1 through 45           507         -36 through 65         -36 through -1         1 through 65           50	492	-50 through 168		
494         -19 through 115         -19 through -1         1 through 115           495         -16 through 69         -16 through -1         1 through 69           496         -29 through 263         -29 through -1         1 through 263           497         -56 through 66         -56 through -1         1 through 66           498         -28 through 31         -28 through -1         1 through 31           499         -13 through 86         -13 through -1         1 through 86           500         -13 through 86         -13 through -1         1 through 86           501         -25 through 83         -25 through -1         1 through 83           502         -15 through 168         -15 through -1         1 through 168           503         -15 through 83         -15 through -1         1 through 83           504         -57 through 126         -57 through -1         1 through 126           505         -14 through 126         -14 through -1         1 through 126           506         -14 through 45         -14 through -1         1 through 45           507         -36 through 65         -36 through -1         1 through 65           508         -55 through 286         -55 through -1         1 through 66           50	493	-15 through 201		
495         -16 through 69         -16 through -1         1 through 69           496         -29 through 263         -29 through -1         1 through 263           497         -56 through 66         -56 through -1         1 through 263           498         -28 through 31         -28 through -1         1 through 31           499         -13 through 86         -13 through -1         1 through 86           500         -13 through 86         -13 through -1         1 through 86           501         -25 through 83         -25 through -1         1 through 83           502         -15 through 168         -15 through -1         1 through 168           503         -15 through 126         -15 through -1         1 through 83           504         -57 through 126         -57 through -1         1 through 83           505         -14 through 126         -14 through -1         1 through 126           506         -14 through 45         -14 through -1         1 through 45           507         -36 through 65         -36 through -1         1 through 65           508         -55 through 286         -55 through -1         1 through 65           509         -42 through 66         -42 through -1         1 through 54           510	494	\ -19 through 115		
496       -29 through 263       -29 through -1       1 through 263         497       -56 through 66       -56 through -1       1 through 263         498       -28 through 31       -28 through -1       1 through 31         499       -13 through 86       -13 through -1       1 through 86         500       -13 through 86       -13 through -1       1 through 86         501       -25 through 83       -25 through -1       1 through 83         502       -15 through 168       -15 through -1       1 through 168         503       -15 through 83       -15 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 83         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 66         509       -42 through 66       -42 through -1       1 through 54         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 102       -28 through -1       1 through 102 <tr< td=""><td>495</td><td>-16 through 69</td><td></td><td></td></tr<>	495	-16 through 69		
497       .56 through 66       .56 through -1       1 through 66         498       .28 through 31       .28 through -1       1 through 31         499       .13 through 86       .13 through ·1       1 through 86         500       .13 through 86       .13 through ·1       1 through 86         501       .25 through 83       .25 through ·1       1 through 83         502       .15 through 168       .15 through ·1       1 through 168         503       .15 through 126       .57 through ·1       1 through 83         504       .57 through 126       .57 through ·1       1 through 126         505       .14 through 126       .14 through ·1       1 through 126         506       .14 through 45       .14 through ·1       1 through 45         507       .36 through 65       .36 through ·1       1 through 65         508       .55 through 286       .55 through ·1       1 through 66         509       .42 through 66       .42 through ·1       1 through 54         510       .26 through 54       .26 through ·1       1 through 114         512       .28 through 102       .28 through ·1       1 through 102         513       .62 through 137       .62 through ·1       1 through 137 <td>496</td> <td></td> <td></td> <td></td>	496			
498       -28 through 31       -28 through -1       1 through 31         499       -13 through 86       -13 through -1       1 through 86         500       -13 through 86       -13 through -1       1 through 86         501       -25 through 83       -25 through -1       1 through 83         502       -15 through 168       -15 through -1       1 through 168         503       -15 through 83       -15 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 66         509       -42 through 66       -42 through -1       1 through 54         510       -26 through 54       -26 through -1       1 through 14         511       -44 through 114       -44 through -1       1 through 102         513       -62 through 102       -28 through -1       1 through 137	497	-56 through 66		
499       -13 through 86       -13 through -1       1 through 86         500       -13 through 86       -13 through -1       1 through 86         501       -25 through 83       -25 through -1       1 through 83         502       -15 through 168       -15 through -1       1 through 168         503       -15 through 83       -15 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 14         511       -44 through 114       -44 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	498			
500         -13 through 86         -13 through -1         1 through 86           501         -25 through 83         -25 through -1         1 through 83           502         -15 through 168         -15 through -1         1 through 83           503         -15 through 83         -15 through -1         1 through 83           504         -57 through 126         -57 through -1         1 through 126           505         -14 through 126         -14 through -1         1 through 126           506         -14 through 45         -14 through -1         1 through 45           507         -36 through 65         -36 through -1         1 through 65           508         -55 through 286         -55 through -1         1 through 286           509         -42 through 66         -42 through -1         1 through 66           510         -26 through 54         -26 through -1         1 through 54           511         -44 through 114         -44 through -1         1 through 114           512         -28 through 102         -28 through -1         1 through 137           514         -62 through 137         -62 through -1         1 through 137	499			
501       -25 through 83       -25 through -1       1 through 83         502       -15 through 168       -15 through -1       1 through 168         503       -15 through 83       -15 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	500			
502         -15 through 168         -15 through -1         1 through 168           503         -15 through 83         -15 through -1         1 through 83           504         -57 through 126         -57 through -1         1 through 126           505         -14 through 126         -14 through -1         1 through 126           506         -14 through 45         -14 through -1         1 through 45           507         -36 through 65         -36 through -1         1 through 65           508         -55 through 286         -55 through -1         1 through 286           509         -42 through 66         -42 through -1         1 through 66           510         -26 through 54         -26 through -1         1 through 54           511         -44 through 114         -44 through -1         1 through 114           512         -28 through 102         -28 through -1         1 through 137           514         -25 through 137         -62 through -1         1 through 137	501			
503       -15 through 83       -15 through -1       1 through 83         504       -57 through 126       -57 through -1       1 through 126         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 137         513       -62 through 137       -62 through -1       1 through 137	502			
504       -57 through 126       -57 through -1       1 through 126         505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 65         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	503			
505       -14 through 126       -14 through -1       1 through 126         506       -14 through 45       -14 through -1       1 through 126         507       -36 through 65       -36 through -1       1 through 45         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	504			
506       -14 through 45       -14 through -1       1 through 45         507       -36 through 65       -36 through -1       1 through 45         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	505		·	
507       -36 through 65       -36 through -1       1 through 45         508       -55 through 286       -55 through -1       1 through 286         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137	506			
508       -55 through 286       -55 through -1       1 through 65         509       -42 through 66       -42 through -1       1 through 66         510       -26 through 54       -26 through -1       1 through 54         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137				
509       -42 through 66       -42 through -1       1 through 286         510       -26 through 54       -26 through -1       1 through 66         511       -44 through 114       -44 through -1       1 through 114         512       -28 through 102       -28 through -1       1 through 102         513       -62 through 137       -62 through -1       1 through 137         514       -25 through 15F       -25 through -1       1 through 137				
510     -26 through 54     -26 through -1     1 through 66       511     -44 through 114     -44 through -1     1 through 114       512     -28 through 102     -28 through -1     1 through 102       513     -62 through 137     -62 through -1     1 through 137       514     -25 through 157     -25 through -1     1 through 137	<b></b>			1 through 286
511     -44 through 114     -44 through -1     1 through 54       512     -28 through 102     -28 through -1     1 through 102       513     -62 through 137     -62 through -1     1 through 137       514     -25 through 155     -25 through -1     1 through 137				1 through 66
512 -28 through 102 -28 through -1 1 through 102 513 -62 through 137 -62 through -1 1 through 137	<del></del>			1 through 54
513 -62 through 137 -62 through -1 1 through 102 514 -25 through 137 -62 through -1 1 through 137				
514 25 shaped 155				1 through 102
314 -25 through 155 -25 through -1 1 through 155				1 through 137
t wadgi 100	514	-25 through 155	-25 through -1	1 through 155

-120-

TABLE VI

ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignatTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	SignalTag 67-90
57	ATCC # 98921	SignalTag 121-144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 9892D	SignalTag 67-90
60	ATCC # 98920	SignalTag 67-90
61	ATCC # 98923	SignalTag 44-66
62	ATCC # 98923	SignalTag 44-66
63	ATCC # 98923	SignalTag 44-66
64	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
65	ATCC # 98923	SignalTag 44-66
66	ATCC # 98921	SignalTag 121-144
67	ATCC # 98920	SignalTag 67-90
58	ATCC # 98920	SignalTag 67-90
69	ATCC # 98921	SignalTag 121-144
70	ATCC # 98921	SignalTag 121-144
71	ATCC # 98921	SignalTag 121-144
72	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
3	ATCC # 98923	SignalTag 44-66

74	ATCC # 98923	SignalTag 44-66
75	ATCC # 98920	SignalTag 67-90
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
78	ATCC # 98921	SignalTag 121-144
79	ATCC # 98923	SignalTag 44-66
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
81	ATCC # 98921	SignalTag 121-144
82	ATCC # 98920	SignalTag 67-90
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
84	ATCC # 98923	SignalTag 44-66
85	ATCC # 98923	SignalTag 44-66
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
87	ATCC # 98923	SignalTag 44-66
88	ATCC # 98923	SignalTag 44-66
89	ATCC # 98923	SignalTag 44-66
90	ATCC # 98923	SignalTag 44-66
91	ATCC # 98923	SignalTag 44-66
92	ATCC # 98920	SignalTag 67-90
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
94	ATCC # 98923	SignalTag 44-66
95	ATCC # 98923	SignalTag 44-66
96	ATCC # 98920	SignalTag 67-90
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
98	ATCC # 98921	SignalTag 121-144
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
100	ATCC # 98921	SignalTag 121-144
101	ATCC # 98920	SignalTag 67-90
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
105	ATCC # 98921	SignalTag 121-144
106	ATCC # 98920	SignalTag 67-90
107	ATCC # 98920	SignalTag 67-90
108	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
109	ATCC # 98923	SignalTag 44-66
110	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120

111	ATCC # 98922 ATCC # 98920	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120. SignalTag 67-90
		SignalTag 67 00
110		Oliman ag 07-50
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

·123<u>-</u>

TABLE VII

	. TABLE VII		
Internal designation number	SEQ ID NO	Type of sequence	
20-5-2-C3-CL0_4	40	DNA	
20-8-4-A11-CL2_6	41	DNA	
21-1-4-F2-CL11_1	42	DNA	
22·11·2·H9-CL1_1	43	DNA	
25-7-3-D4-CLO_2	44	DNA	
26-27-3-D7-CLO_1	45	DNA	
26-35-4-H9-CL1_1	46	DNA	
` 26-45-2-C4-CL2_6	47	DNA	
27-1-2-B3-CL0_1	48	DNA	
27-1-2-B3-CLO_2	49	DNA	
27-19-3-G7-CL11_2	50	DNA	
33-10-4-E2-CL13_4	51	DNA	
33-10-4-H2-CL2_2	52	DNA	
33-110-4-A5-CL1_1	53	DNA	
33-13-1-C1-CL1_1	54	DNA	
33-30-2-A6-CLO_1	55	DNA	
33-35-4-F4-CL1_2	56	DNA	
33-35-4-61-CL1_2	57	DNA	
33-36-3-E2-CL1_1	58	DNA	
33-36-3-E2-CL1_2	59	DNA	
33-36-3-F2-CL2_2	60	· DNA	
33-4-2-G5-CL2_1	61	DNA	
33-49-1-H4-CL1_1	62	DNA ·	
33-66-2-B10-CL4_1	63	DNA	
33-97-4-68-CL2_2	64	DNA	
33-98-4-C1-CL1_3	-65	DNA .	
47-14-1-C3-CL0_5	66	DNA	
47-15-1-E11-CLO_1	67	DNA	
47-15-1-H8-CLO_2	68	DNA	
48-1-1-H7-CLO_1	69	DNA	
48-1-1-H7-CLO_4	70	DNA	
48-1-1-H7-CLO_5	71	DNA	
48-3-1-H9-CLO_6	72	DNA	
48-54-1-G9-CL2_1	73	DNA	

re vak din di Walander statungken kenandalang satu a krip di sebesakan kadalah di dinakan kenandakan di kanasa Mi

48-54-1-G9-CL3 1	74	-
48-7-4-H2-Cl2_2	74	DNA
	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	. 88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA

		- 125-
30-12-3-G5-CLO_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-45-4-A11-CL1_4	116	DNA
51-1-4-C1-CLO_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	-128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CL0_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CLO_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CLO_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

		-120-
26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CL0_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRŢ
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CL0_2	183	PRT
51-34-3-F8-CLO_2	184	PRT

57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT ,
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
√ 65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CL0_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CL0_3	211	PRT
30-12-3-G5-CLO_1	212	PRT
33-106-2-F10-CL1_3	· 213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

		120-
57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33 11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLD_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CLO_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
20-6-1-D11-FL2	242	DNA
20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA

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		-
33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-B7-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-88-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
51-1-1-G12-FL1	293	DNA
51-1-4-E9-FL3	294	DNA
51-1-4-E9-FL2	295	DNA
	<u></u>	

Continued Control of the Control of

		100-
51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-D12-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
58-44-2-B3-FL3	326	DNA
58-45-3-H11-FL1	327	DNA
58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
60-16-3-A6-FL1	330	DNA
60-17-3-68-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

65-4-4-H3-FL1	333	DNA
74-3-1-B9-FL1	334	DNA
76-4-1-G5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
76-30-3-B7-FL1	338	DNA
77-5-1-C2-FL1	339	DNA
77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

57-25-1-F10-FL2	370	DNA
58-19-3-D3-FL1	371	DNA
58-34-3-C9-FL2	372	DNA
58-48-4-E2-FL2	373	DNA
76-21-1-C4-FL1	374	DNA
78-26-2-H7-FL1	375	DNA
77-20-2-E11-FL1	376	DNA
47-1-3-F7-FL2	377	DNA
20-6-1-D11-FL2	378	PRT
20-8-4-A11-FL2	379	PRT
22-6-2-C1-FL2	380	PRT
22-11-2-H9-FL1	381	PRT
23-8-3-B1-FL1	382	PRT
24-3-3-C6-FL1	383	PRT
24-4-1-H3-FL1	384	PRT
26-45-2-C4-FL2	385	PRT
26-48-1-H10-FL1	386	PRT
26-49-1-A5-FL2	387	PRT
30-6-4-E3-FL3	388	PRT
33-6-1-G11-FL1	389	PRT
33-8-1-A3-FL2	390	PRT
33-11-3-C6-FL1	391	PRT
33-14-4-E1-FL1	392	PRT
33-21-2-D5-FL1	393	PRT
33-26-4-E10-FL1	394	PRT
33-27-1-E11-FL1	395	PRT
33-28-4-D1-FL1	396	PRT
33-28-4-E2-FL2	397	PRT
33-30-4-C4-FL1	398	PRT
33-35-4-F4-FL1	399	PRT
33-36-3-F2-FL2	400	PRT
33-52-4-F9-FL2	401.	PRT
33-52-4-H3-FL1	402	PRT
33-59-1-B7-FL1	403	PRT
33-71-1-A8-FL1	404	PRT
33-72-2-B2-FL1	405	PRT
33-105-2-C3-FL1	406	PRT

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33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
. 48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	. PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT

		104
51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9-4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

77-26-2-F2-FL3	481	PRT	
78-6-2-E3-FL2	482	PRT	
78-7-1-G5-FL2	483	PRT	
78-16-2-C2-FL1	484	PRT	
78-18-3-B4-FL3	485	PRT	
78-20-1-G11-FL1	486	PRT	
78-22-3-E10-FL1	487	PRT	
78-24-2-B8-FL1	488	PRT	
78-24-3-A8-FL1	489	PRT	
78-24-3-H4-FL2	490	PRT	
78-25-1-F11-FL1	491	PRT	
78-26-1-B5-FL1	492	PRT	
78-27-3-D1-FL1	493	PRT	
78-29-1-B2-FL1	494	PRT	
78-29-4-B6-FL1	495	PRT	
14-1-3-E6-FL1	496	PRT	
30-9-1-G8-FL2	497	PRT	
33-10-4-H2-FL2	498	PRT	
33-10-4-H2-FL1	499	PRT	
74-10-3-C9-FL2	500	PRT	
33-97-4-G8-FL3	501	PRT	
33-97-4-G8-FL2	502	PRT	
33-104-4-H4-FL1	503	PRT	
47-2-3-B3-FL1	504	PRT	
47-37-4-G11-FL1	505	PRT	
57-25-1-F10-FL2	- 506	PRT	
58-19-3-D3-FL1	507	PRT	
58-34-3-C9-FL2	508	PRT	
58-48-4-E2-FL2	509	PRT	
76-21-1-C4-FL1	510	PRT	
78-26-2-H7-FL1	511	PRT	
77-20-2-E11-FL1	512	PRT	
47-1-3-F7-FL2	513	PRT	

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## TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature

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## WHAT IS CLAIMED IS:

- A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
  - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48,
   49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48,
   49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140
   and 242-377 which encode the signal peptide.
  - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20
   189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
    - 9. A purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
  - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

cDNA.

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obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

- 14. The method of Claim 13, further comprising the step of isolating said protein.
- 15. A protein obtainable by the method of Claim 14.
- 16. A host cell containing a recombinant nucleic acid of Claim 1.
- 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent
   conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
  - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEO ID NOs: 141-241 and 378-513.

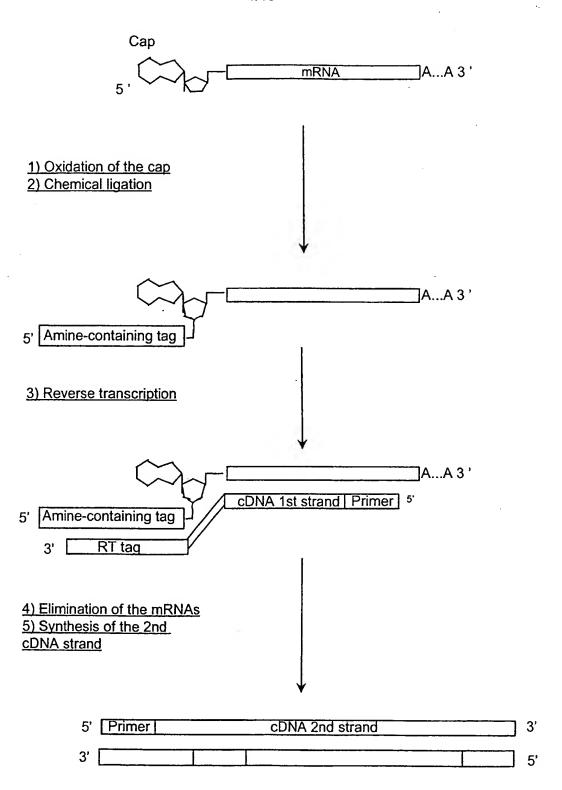
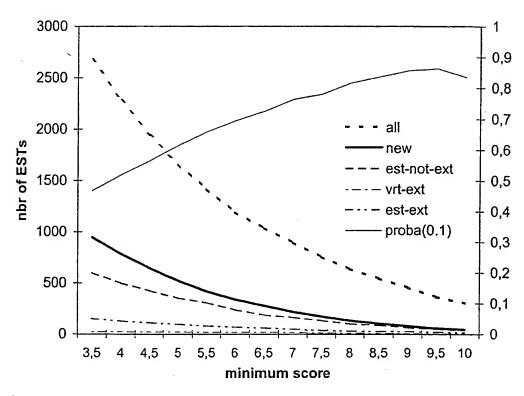


Figure 1

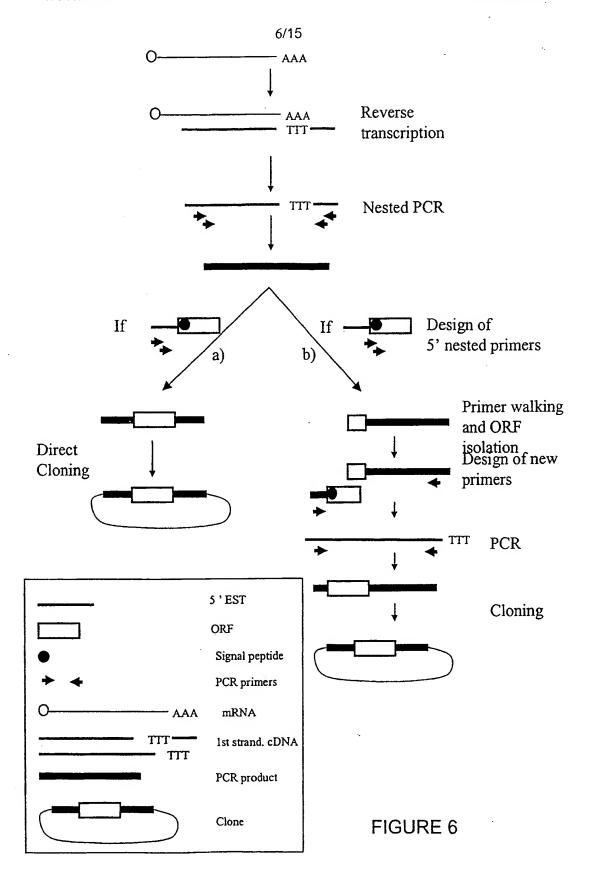
Minimum signal peptide score		false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

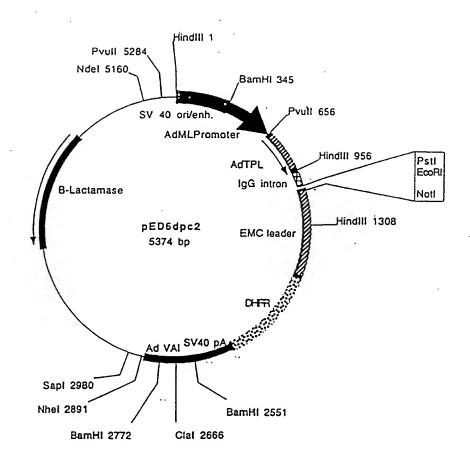
## influence of minimum score on signal peptide recognition



Minimum signal peptide score	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

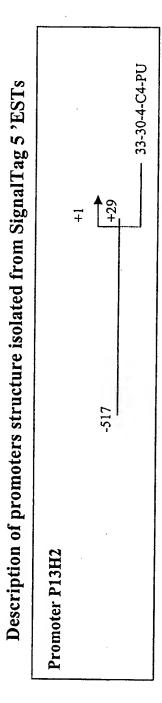
	<del>γ</del>			· · · · · · · · · · · · · · · · · · ·	
Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	. 3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	. 9	1	0	6
Colon	21	11	4	0	o
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	o.
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	. 0	· ō
Large intestine	21	8	4	0	1
Liver	23	9	6	0	o
Lung	24	12	4	0	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	o
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	- 47	27	1	6
Surrenals	15	3	3	.1	0
Testis	131	68	25	1	
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	<b>1</b>	8 2 3
Uterus	28	15	3	0	. 2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150





Plasmid name: pED6dpc2 Plasmid size: 5374 bp

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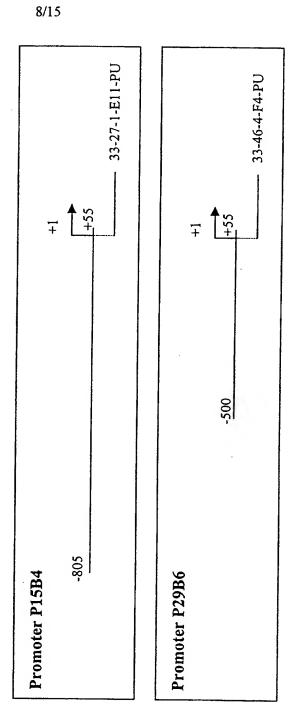


FIGURE 8

WO 99/31236 PCT/IB98/02122

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# Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

## Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	·	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	. 11	GCACACCTCAG
GATA_C	-364	•	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

#### Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	. +	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-5 <b>5</b> 6	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

### Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	•	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

100.0% identity in 125 aa overlap SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

# CLUSTAL W(1.5) multiple sequence alignment

SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKRIFKIDWTLS
SEQ ID NO:	517	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE
SEQ ID NO:	232	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
SEQ ID NO:	174	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL
SEQ ID NO:	175	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
		***********************
SEQ ID NO:		
SEQ ID NO:		KGESQVFKKAVVLHVLPEEPKGTQMLT
SEQ ID NO:		KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE
SEQ ID NO:	175	KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
SEQ ID NO:	517	
SEQ ID NO:	232	
SEQ ID NO:	174	IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN
SEQ ID NO:	175	VTRRKHHCVREGSG
SEQ ID NO:	517	
SEQ ID NO:	232	
SEQ ID NO:	174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ ID NO:	175	
SEQ ID NO:	517	
SEQ ID NO:	232	
SEQ ID NO:	174	GNKSSVNSTVLVKNTKKTNP
SEQ ID NO:	175	

99.6% identity	in 225 aa overlap	٠.
	10 20 30 40 50 60	
SEQ ID NO: 515	PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILA	GLI
	:::::::::::::::::::::::::::::::::::::::	:::
SEQ ID NO: 231	LRVATQEKEGSSGRCMLTLLGLSFILA	
	10 20	30
	70 80 90 100 110 120	
CEO ID NO. E1E	70 100 120 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAI	TDV
SEG ID MO: 212	VOGACIINIFMFX5111KGEMCFFD5EDFAN5UKGGEFNFUFV1EEADIKEDDN1A1	100
SEC ID NO. 231	VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAI	TDV
DEQ ID NO. 231	40 50 60 70 80	90
•	30 140 150 160 170 180	
SEQ ID NO: 515	PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLAS	GRY
-		:::
SEQ ID NO: 231	PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLAS	GRY
	100 110 120 130 140	150
	90 . 200 210 220 230 240	
SEQ ID NO: 515	t LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCW	
	· · · · · · · · · · · · · · · · · · ·	
SEQ ID NO: 231	LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCW	
	160 170 180 190 200	210
	50 260	
	HFPNEFIVETKICOE	
DEG ID NO. 313	::::::::::::::::::::::::::::::::::::::	
SEQ ID NO: 231	HFPNEFIVETKICQE	

99.7% identity in 353 aa overlap MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEO ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEO ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEO ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF ...... SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEO ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEO ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEO ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL

. . . . . .

SEQ ID NO:158 PP

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#### 14/15

98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL SEQ ID NO:519 AS

68.9% identity in 74 aa overlap

SEQ ID NO:514 MMTGRQGRATFQFLPDEARSLPPPKLTDPRLAFVGFLGYCSGLIDNAIRRRPVLLAGLHR

10 20 30 40 50 60

60 70

SEQ ID NO:226 QLLYITAFFLLDIIL

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. WO 99/31236 PCT/IB98/02122

<110> Dumas Milne Edwards, Jean-Baptiste
Duclert, Aymeric
Bougueleret, Lydie

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SECURIO EL LA SERVICIO DE LA CARTA DE LA CARTA DE COMO DE LA CARTA DEL CARTA DEL CARTA DE LA CARTA DE LA CARTA DEL CAR

graphic for the contract of th

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Met Trp Trp Phe	
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Gln Gln Gly Leu Ser Phe Leu Pro Ser Ala Leu Val Ile Trp Thr Ser	
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get get tte ata ttt tea tac att act gea gta aca ete cae cat ata	453
Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu His His Ile	
1 5 10 15	E 0.1
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Lys ctcttcaraa acatgtcttt acaagcatat ctcttgtatt gctttctaca ctgttgaatt	662

374

405

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Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly
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            -10
                                                                      153
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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                        10
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                                                                       201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp
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Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val
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Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn
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                                                 80
                                                                       393
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Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln
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                        90
                                             95
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agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc
                                                                       489
Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
                120
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ctt ccc awt tcc aac ccc ctc tgc cca rgg gaa acc cag gaa gga
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Asp Gln Thr Leu Glu Phe Leu Lys Ile Pro Ser Thr Leu Ala Pro Pro

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atg gac cca tct gtg ccc atc tgg att att ata ttt ggt gtg ata ttt Met Asp Pro Ser Val Pro Ile Trp Ile Ile Ile Phe Gly Val Ile Phe	484
125 130 135	
tgc atc atc ata gtt gca att gca cta ctg att tta tca ggg atc tgg	E22
Cys Ile Ile Val Ala Ile Ala Leu Leu Ile Leu Ser Gly Ile Trp	532
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Pro Leu Asp Met Lys Gly Gly His Ile Asn Asp Ala Phe Met Thr Glu	
190 195 200	
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Asp Glu Arg Leu Thr Pro Leu .	
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<223> matinspector prediction
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<221> protein\_bind

<222> 400..409

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<222> complement (460..470)

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 score 0.963
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<221> protein bind

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Leu Ser Lys Ser Leu Leu Leu Val Pro Ser Ala Leu Ser Leu Leu Leu	٠
-15 -10 -5	144
gcc ctc ctc ctg cct cac tgc cag aag ccc ttt gtg tat gac ctt cac Ala Leu Leu Pro His Cys Gln Lys Pro Phe Val Tyr Asp Leu His	111
1 5 10 15	
gca gtc aag aac gac ttc cag att tgg agg ttg ata tgt gga aga ata	192
Ala Val Lys Asn Asp Phe Gln Ile Trp Arg Leu Ile Cys Gly Arg Ile 20 25 30	
att tgc ctt gat ttg aaa gat act ttc tgc agt agt ctg ctt att tat	240
Ile Cys Leu Asp Leu Lys Asp Thr Phe Cys Ser Ser Leu Leu Ile Tyr	
35 40 45	288
aat ttt agg ata ttt gaa aga aga tat gga agc aga aaa ttt gca tcc Asn Phe Arg Ile Phe Glu Arg Arg Tyr Gly Ser Arg Lys Phe Ala Ser	200
50 55 60	

•	
ttt ttg ctg ggt acc tgg gtt ttg tca gcc tta ttt gac ttt ctc Phe Leu Leu Gly Thr Trp Val Leu Ser Ala Leu Phe Asp Phe Leu 65	c ctc 336 u Leu
att gaa gct atg cag tat ttc ttt ggc atc act gca gct agt aat Ile Glu Ala Met Gln Tyr Phe Phe Gly Ile Thr Ala Ala Ser Ass	t ttg 384 n Leu
80 85 90 CCC tot gga tha ato the tot tot gct tot tot gag act and Pro Ser Gly Leu Ile Phe Cys Cys Ala Phe Cys Ser Glu Thr Lys	95 a ctc 432
100 105 110 ttc tta tca aga caa gct atg gca gag aac ttt tcc atc taataaa	0
Phe Leu Ser Arg Gln Ala Met Ala Glu Asn Phe Ser Ile 115 120	
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gatacggcgc ccagcggggt cagaaagcaa cattgaatgc agaagaa atg gcg Met Ala 1	gac 176
ttc tac aag gaa ttt tta agt aaa aat ttt cag aag cgc atg tat Phe Tyr Lys Glu Phe Leu Ser Lys Asn Phe Gln Lys Arg Met Tyr 5 10	tat 224 Tyr
aac aga gat tgg tac aag cgc aat ttt gcc atc acc ttc ttc atg Asn Arg Asp Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met	Gly
aaa gtg gcc ctg gaa agg att tgg aac aag ctt aaa cag aaa caa	35 aag 320
Lys Val Ala Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln 40 45 50	
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aggaagcaga tggagctcct ttcacagggg ctctgagaaa aactggagcc gatc	tcaaga 432
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					_								-20		
cgg a	ac ctg sn Leu	cgc Ara	acc Thr	gcg	Leu	att Ile	ttc Phe	ggc	ggc	ttc Phe	atc Ile	tcc	Leu	atc Ile	104
_		-15					-10	_	_			-5			
	cc gcc la Ala														152
GIY A.	1	PIIC	TAT	PIO	5	ıyı	FIIC	Arg	FLO	10	Mec	Arg	neu	GIU	
	ac aag														200
G1u T	yr Lys	гуѕ	GIU	20	АТА	11e	Asn	Arg	A1a 25	GIY	шe	vaı	GIN	30	
	tg cag														248
Asp V	al Gln	Pro	Pro 35	GIY	Leu	Lys	Val	Trp	Ser	Asp	Pro	Phe	G1y 45	Arg	
aaa t	gagaggg	get g		cago	t ct	gati	taaga		ggaga	ittt	cttc	atg			301
Lys	tctgc a	at aac	otac	ים מכ	cagt	caco	r tca	ccac	aga	atga	caac	rta (	gagaa	адалала	361
															421
30 30 30											481 541				
											601				
	ctcgg g														661 721
	ccatg o														721
atgaagcaag tcaaactaga tgcatacact tgtgtagaaa tcaataatca attaatagaa															
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	Ala	Met	Val	Thr		Pro	Ala	Ser	Ala	Ala	Pro	Met	Gly	Gly	Pro	•
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						gag										148
GIU	Leu	Ala	GIN 10	Hls	GIU	Glu	Leu		Leu	Leu	Phe	His		Thr	Leu	
can	cta	aac		000	ata	224	aat.	15	+				20		<b>.</b>	100
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0111		25	0111	ALG	Бец	ASII	30	VAI	ıyı	Arg	IIII	35	Giu	GIY	пр	
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Leu	Thr	Lys	Ala	Arg	Asn	Ser	Leu	Gly	Leu	Tyr	Gly	Arg	Thr	Ile	Glu	
	40					45					50					
ctc	ctg	999	cag	gag	gtc	agc	cgg	ggc	cgg	gat	gca	gcc	cag	gaa	ctt	292
Leu	Leu	Gly	Gln	Glu		Ser	Arg	Gly	Arg		Ala	Ala	Gln	Glu	Leu	
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cgg	gca	agc	ctg	ttg	gag	act	cag	atg	gag	gag	gat	att	ctg	cag	ctg	340
Arg	Ата	ser	ьeu		GIu	Thr	GIn	Met		Glu	Asp	Ile	Leu		Leu	
cac	.cca	<b>~~~</b>	~~~	75	aat		~+~	a+a	80					85		200
Gln	Δla	Glu	Ala	Thr	Ala	gag Glu	yra Val	Leu	999	gag	gcg	gcc	cag	gca	cag	388
0.1.11	niu	OIU	90	1111	VIG	GIU	Vai	95	GIY	Giu	val	AId	100	AIA	GIN	
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Lys	Val	Leu	Arq	Asp	Ser	Val	Gln	Ara	Leu	Glu	Val	Gln	Leu	Arg	Ser	130
•		105		•			110	5				115				
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-10 -5 1 .atc aaa agc agc cct gtt ttc caa ata cct aaa aac gac gac att cct	146
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gag caa gat agt ctg gga ctt tca aat ctt cag aag agc caa atc cag Glu Gln Asp Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln 25 30 35	194
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70 75 80 gga aca tac ttt ttg cag agg tct gca aag cag tct gta aaa ttt cag	386
Gly Thr Tyr Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln	
85 90 95 100	
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tcgtgcgtgt ggctggattg cccagggaag aagcagatgc tctctatgaa gctctgaaga atcttacacc atatgtggct attgaggaca aagac atg cag caa aaa gaa cag  Met Gln Gln Lys Glu Gln	293
-70 -65	341
cag ttt agg gag tgg ttt ttg aaa gag ttt cct caa atc aga tgg aag.  Gln Phe Arg Glu Trp Phe Leu Lys Glu Phe Pro Gln Ile Arg Trp Lys  -60  -55  -50	3.1
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Lare	Val	Hig	Ara	Glv	Cvs	Val-	Tle	Ala	Asn	Val	Val	Ser	Glv	Ser	Thr	
Lys	· u =	-30	••••	41	-,-		-25					-20	•			
-	atc		tet	atc	att	aac		ato	tta	gca	сса	_	aca	qca	aaa	485
gge	Ile	teu	200	37-1	Tla	23	Val	Mot	Lou	Ala	Dro	Dhe	Thr	Δla	G) iv	
GIY		Leu	Ser	٧ал	TIE		vai	Mec	beu	AIA		FIIC	1111	ALU	CII	
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ctg	agc	ctg	agc	att	act	gca	gct	<u>a</u> aa	gta	999	ctg	gga	ata	gca	2	535
Leu	Ser	Leu	Ser	Ile	Thr	Ala	Ala	Gly	Val	Gly	Leu	GIA	He		ser	
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Ala	Thr	Ala	Gly	Ile	Ala	Ser	Ser	Ile	Val	Glu	Asn	Thr	Tyr	Thr	Arg	
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Ser	Ala	Glu	Leu	Thr	Ala	Ser	Arq	Leu	Thr	Āla	Thr	Ser	Thr	Asp	Gln	
501		35					40					45		-		
++~	gag		`++=	200	asc.	att		cat	gac	atc	aca		aat	ata	ctt	677
Tan	Glu	31-	ton	299	300	Tla	Lau	Uic	yen ago	Tle	Thr	Dro	Δen	Val	Len	
ren		ALG	Leu	Arg	Asp		Dea	UIS	nsp	110	60	rio	UDII	V (4.1	Dog	
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tcc	ttt	gca	ctt	gat	ttt	gac	gaa	gcc	aca	aaa	atg	acc	geg	aat	gat	123
Ser	Phe	Ala	Leu	Asp	Phe	Asp	Glu	Ala	Thr		Met	11e	Ala	Asn		
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Val	His	Thr	Leu	Arg	Arg	Ser	Lys	Ala	Thr	Val	Gly	Arg	Pro	Leu	Ile	
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Δla	Trp	Ara	Tvr	Val	Pro	Tle	Asn	Val	Val	Glu	Thr	Leu	Arq	Thr	Arq	
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999	Ala	Dwa	mb	299	Tla	77-7	۵ya	Lac	yea Val	Ala	722	Aen	Len	Glv	Lvs	
GIA	Ala		Inr	Arg	116	vai			vai	Ala	Arg	125		Gry	шуз	
		115					120									917
gcc	act	tca	ggt	gtc	CTC	gtt	grg	ctg	gat	gta	gcc	aac	7	gra	Caa	311
Ala	Thr	Ser	Gly	Val	Leu			ren	Asp	vaı			Leu	vai	GIII	
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145					150					155					160	
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Leu	Arg	Gln	Trp	Ala	Gln	Glu	Leu	Glu	Glu	Asn	Leu	Asn	Glu	Leu	Thr	
	_		_	165					170					175		
cat	atc	cat	cag	agt	cta	aaa	qca	qqc	tag	qccc	aat	tgtt	gegg	ga	•	1060
	Ile									_		_		•		
			180			-,		185								
an+	Carr	gac			as a	ggan	taar			atoo	cac	aada	aco	tgga	ttgtga	1120
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aga	+	acy	gaca		20 2	geee	++~+	·	antt	test		čact	tat	cact	tcccca	1240
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ate	annar	atc	acco	1220	ta d	teat	catai	cor at	atict	CCCC	ta	acac	ccta	qctt	taaaat	2020
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 His
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WO 99/31236

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150

145

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Ala		Lys	Val	Lys	Cys		Pro	ıyr	Ala	vaı	Leu	ьeu	GIU	Ala	10	
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Glu	Val		Tyr	Ser	Ile	Gly		Asp	Ile	GIn	Arg		Asp	Leu	ser	
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Ald	60	Ala	Arg	1111	пеп	65	Giu	rrp	Cy 5	· uı	70	U, D	0.10			
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Gln	Gln	Leu	Gly		Lys	Gln	Gln	Ile			GIu	val	Ala	Asn 105		
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Tare	Twe	Thr	Tle	Lve	Val	Thr	Thr	Ala	Ala	Ala	Ala	Ala	Ala	Thr	Ser	
пуз	БуЗ	1111	110		• • • •			115					120			
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Gln	Asp	Pro	Glu	Gln	His	Leu	Thr	Glu	Lev	Arg	Glu	Pro	Ala	Pro	Gly	
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Thr			Arg	Gin	Pro			гуу	Ala	ser	ъув 150		гуу	. Сту	Leu	
cas	140				. stt	145	•	· aac	rtco	ı aat			act	atca	tttcct	893
Ara	. G] v	Ser	Ala	Lvs	Ile	Tre	Ser	Lvs	Ser	Asn	1			JJ		
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Thr Tyr Asn Lys His Ile Asn Ile Ser Phe His Arg
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GIII	шуз	Giu	160	nr 9	лти	1111	**** 9	165			_,_		170	-2-			
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gta	aag	aat	tta	gaa	gca	aat	agt	gca	tta	- 661	-	991	aca	Coa	gaa	050	
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Lys	Gln	Thr	Lys	Ser 225		Phe	Ile	:									
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	2220	***	+9**	+~~~	at 5	2026	+20+		+++	tras		ttas	tta	caaa	agaata	968	
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                         -35
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 Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His Asn
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                       125
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で発送機関のには、もののはできないに いっこ

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Met Cy	s Ser	Val	His	Pro	Cys	Arg	His	Ala		Val	Met	Lys	Lys	Ile	
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tat ga	ic tac	.aca	aga	Uic	Dha	Thr	Met	Laa	Lyaas	Jag (	agea	Luuu			
Tyr As	sp 191 250		Arg	nis	PIIC	255	Mec								
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Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly Ser -15 -10 -5 1	
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Thr Val Leu Gly Leu Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys 45 50 7 55 60	
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Phe Ser Ala Val Phe Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu	
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461

521

568

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cct tca gct tcc taaattctgt gtctgtgact ttcgaagttt tttaaacctc Pro Ser Ala Ser 55	
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gaa	gat	gtg	gcc	acg	TCC	caa	gac	gac	Cyc	Tur	Lve	Dhe	Δla	Tle	Ser	
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	ser	MIG	Arg	Gry		Giu	шеш	My	БСС		DCu	JCI	110	Deu	-5		
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Glv	Ala	Gln	Pro	Gln	Gln	Glu	Pro	Leu	Ala	Leu	Val	Phe	Arg	Phe	Glv		
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ren	ьeu	GIU		Cys	HIS	ser	vai		руу	GIU	vai	vai		Den	GIY		
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		Lys															
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Tlo	Cys	Glu	712	Ten	Len	Jac	Gln	722	Dhe	Dhe	Acn	Glv	Tle	GJV	Δsn	
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	ctg															3//
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Lys	Ala	Arg	Ser	Val	Leu	Glu	Ala	Leu	Gln		His	Arg	Pro	Ser		
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Glu	Leu	Thr	Leu	Ser	Gln	Lys	Ile	Arg	Thr	Lys	Leu	Gln	Asn	Pro	Asp	
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yac	Arg	Tic	990	200	The	Tlo	TY5	Dho	Cla	222	yer	Dro	994 61v	Dro	Len	000
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	CCC															713
Ата	Pro	гÀг	GIA	_	гÀг	ser	Arg	гуя		пås	Ser	цуs	Ald		GIII	
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Leu	Ser	Pro		Asp	Arg	vaı	GIU		Ala	ьеи	Pro	Pro		гÀг	Ala	
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cct	ttct	tat		ttac	cc t	acat	ctaa	a aa	+~+~	aatt	+++	מממא	aca .	aaca	atatct	1261
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                                                -65
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Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly Val Ser Leu Pro Gly
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                                             -50
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Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile Leu Ser Asp Ser Ser
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Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln Ser Cys Gln Met Asn
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aac ctg cca cat ctg cag gtg gta gga cta aca tgg ggt cat ata tct
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Asn Leu Pro His Leu Gln Val Val Gly Leu Thr Trp Gly His Ile Ser
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Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile Ile Leu Ala Ser Asp
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Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile Leu Ala Thr Ile Tyr
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Phe Leu Met His Lys Asn Pro Lys Val Gln Leu Trp Ser Thr Tyr Gln
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Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His Thr Val Glu Met Leu
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Val Ile Ser Phe Ala Lys Asp Ser Leu
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-40					-35					-30				000		733
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Ala	Leu	Arg	Pro -5	ctg Leu	Val	Leu	Gly	Gly 1	Asn	Gln	Leu	Val 5	Ile	He	Val	
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77-1	u u	To	Mot	999	, yac	Tle	Let	CVS	. Acr	Asr	G)	z Sei	r Lei	ı Lei	Leu	
val		, re	ı ne ı	. Gly	Ash	55		. c <sub>j</sub> .			60	,		-	•	
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65					70						, ~+·	~ ~+	a	n c=		349
	c aaa	<b>3</b> 999	g gag	gago	: cag	gro	י דנו	, ad	ad <sup>©</sup>	יוא פ	9 94	9 96	1 TA	, u:	t gtg	3.3
cto					- 1217	ı val	. צתפ	= uy	ъπλ	s Ale	ı va.	r Ag	r na	n ur	· • a.	
Lei	ı Ly:	s Gl	y Gl		. 611									Q.E		
Lei	ı Ly:			85					90					95		397
Lei	Ly:	a qa	a dad	85 ccc	aaa	a gac	g cto	c at	90 g gto	c cat	t gt	g gg	t gg	95 a tt	g att	397
Lei	Ly:	a qa	g gaq	85 g cco u Pro	aaa	a gac	g cto	c ato	90 g gto t Vai	c cat	t gt	g gg	t gg y Gl	95 a tt y Le		397
Lei Cti Lei	t cca	a gag	g gag u Gli	85 g cco u Pro	aaa Lys	a gag s Glu	g cto	c ato	90 g gto t Vai	c cat	t gtg	g gg 1 Gl	t gg y Gl ll	95 a tt y Le 0	g att u Ile	
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gy je

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-20 -15  ctc ttc ttc ttt ctc ttc ctc ctc acc agg ggc tca ctt tct cca aca  Leu Phe Phe Phe Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr -10 -5 1 5	99
aaa tat aac ctt ttg gag ctc aag gag tct tgc atc cgg aac cag gac Lys Tyr Asn Leu Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp 10 15 20	147
tgc gag act ggc tgc tgc caa cgt gct cca gac aat tgc gag tcg cac Cys Glu Thr Gly Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His 25 30 35	195
tgc gcg gag aag ggg tcc gag ggc agt ctg tgt caa acg cag gtg ttc Cys Ala Glu Lys Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe 40 45 50	243
ttt ggc caa tat aga gcg tgt ccc tgc ctg cgg aac ctg act tgt ata Phe Gly Gln Tyr Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile 55 60 65	291
tat tca aag aat gag aaa tgg ctt agc atc gcc tat ggc cgt tgt cag Tyr Ser Lys Asn Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln 70 75 80 85	339
aaa att gga agg cag aag ttg gct aag aaa atg ttc ttc tagtgctccc Lys Ile Gly Arg Gln Lys Leu Ala Lys Lys Met Phe Phe 90 95	388
teettettge tgeeteetee teeteeacet geteteetee etaceeagag etetgtgtte accetgttee ceagageete caccatgagt ggagggaagt ggggagtgat tgaaataaag agetttttea atgaaaaaaa aaaaaaaaaa	448 508 542
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atc cta tgt ttc ctt ctt cct cat cat cgt ctt cag gaa gcc aga cag Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg Gln 5 10	107
att caa gta ttg aag atg ctg cca agg gaa aaa tta aga aga aga gaa Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg Glu 20 25 30	155
gag aga aaa caa ata aat ggg aaa aaa gaa agg aca aaa tat gaa aca Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu Thr 35 40	203
cca aga aaa aga gaa gga aaa aaa aaa Pro Arg Lys Arg Glu Gly Lys Lys Lys 50 55	233

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<222> 573..578
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<222> 607..660
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                                                                      112
gagaggggag atcactcttt tg atg gtg gcc ctg aac ctc att ctg gtt ccc
                         Met Val Ala Leu Asn Leu Ile Leu Val Pro
                                          -10
tgc tgc gct gct tgg tgt gac cca cgg agg atc cac tcc cag gat gac
                                                                      160
Cys Cys Ala Ala Trp Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp
                                                                      208
gtg ccc cgt agc tct gct gct gat act ggg tct gcg atg cag cgg cgt
Val Pro Arg Ser Ser Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg
                            20
gag gcc tgg gct ggt tgg aga agg tca caa ccc ttc tct gtt ggt ctg
                                                                      256
Glu Ala Trp Ala Gly Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu
                        35
                                                                       304
cct tct gct gaa aga ctc gag aac caa cca ggg aag ctg tcc tgg agg
Pro Ser Ala Glu Arg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg
                    50
                                        55
                                                                       350
tee etg gte gga gag gga tat aga ate tgt gae ete tgacaactgt
Ser Leu Val Gly Glu Gly Tyr Arg Ile Cys Asp Leu
                65
gaagccaccc tgggctacag aaaccacagt cttcccagca attattacaa ttcttgaatt
                                                                       410
                                                                       470
ccttggggat tttttactgc cctttcaaag cacttaagtg ttagatctaa cgtgttccag
                                                                       530
tgtctgtctg aggtgactta aaaaatcaga acaaaacttc tattatccag agtcatggga
                                                                       590
gagtacaccc tttccaggaa taatgttttg ggaaacactg aaatgaaatc ttcccagtat
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Leu	Cys	Leu	Pro	Arg	Pro	Glu	Ala	Arg	Glu		Pro	Ile	Pro	Val	Pro		
-55					-50					-45					-40		
cca	agg	ggc	ctg	ggt	gct	999	gag	999	tca	ggt	agt	cca	gtg	cgt	cca	15	1
Pro	Arg	Gly	Leu		Ala	Gly	Glu	Gly		Gly	Ser	Pro	Vai	-25	Pro		
				-35				<b>.</b>	-30			-+-	<b>~~</b>		atc	19	q
cct	gta	tcc	acc	tgg	ggc	CCT	agc	tgg	gcc	cag	Ton	tou	yac Arn	cor	ycc val	1)	
Pro	Val	Ser	Thr	Trp	GIÀ	Pro	ser	-15	Ата	GIII	Leu	Dea	-10	Ser	vai		
			-20			~~~	~+~		250	CaG	ac 2	atc		tcc	acc	24	7
cta	tgg	ctg	999 Gly	gca	CLA	Clar	Lou	Thr	Tla	Gla	Ala	Val	Dhe	Ser	Thr		
ьeu	Trp	ьеи -5	GIY	Ala	ьeu	GIÀ	1	1111	116	GIII	5	vai	1110				
·			gcc	a+ <b>a</b>	ata	cta	_	cta	atc	adc		ctc	acc	ttt	gac	29	5
act	gge	Dro	Ala	Leu	Len	Len	Len	Len	Val	Ser	Phe	Leu	Thr	Phe	Asp		_
10	GIY	PIO	AIA	Deu	15	БСи	пси	<u> </u>	, u I	20					25		
	ctc	cat	agg	ccc		aat	cac	act	cta		cag	cac	aaa	ctt		34	3
Len	LAN	Die	Arg	Dro	Δla	Glv	His	Thr	Len	Pro	Gln	Ara	Lvs	Leu	Leu		
пец	пси	1113	AI 9	30	niu	017			35			5	-1-	40			
acc	agg	aac	cag		caq	aαα	acc	aat	gaa	aat	cct	qqa	caq	caq	gag	39	1
Thr	Ara	GJV	Gln	Ser	Gln	Glv	Ala	Glv	Glu	Gly	Pro	Gly	Gln	Gln	Glu		
	5	7	45			•		50		-		-	55				
act	cta	ctc	ctg	caa	atq	ggt	aca	gtc	tca	gga	caa	ctt	agc	ctc	cag	43	9
Ala	Leu	Leu	Leu	Gln	Met	Gly	Thr	Val	Ser	Gly	Gln	Leu	Ser	Leu	Gln		
		60				•	65					70					
gac	gca	ctg	ctg	ctg	ctg	ctc	atg	999	ctg	ggc	ccg	ctc	ctg	aga	gcc	48	37
Asp	Ala	Leu	Leu	Leu	Leu	Leu	Met	Gly	Leu	Gly	Pro	Leu	Leu	Arg	Ala		
	75					80					85						
tgt	ggc	atg	ccc	ttg	acc	ctg	ctt	ggc	ctg	gct	ttc	tgc	ctc	cat	cct	53	35
Cys	Gly	Met	Pro	Leu	Thr	Leu	Leu	Gly	Leu			Cys	Leu	His	Pro		
90					95					100					105		
tgg	gcc	tga	gagc	ccc	tccc	caca	ac t	cagt	gtcc	t tc	aaat	atac	aat	gacc	acc	59	91
Trp	Ala															٠,	<b>.</b> =
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att gag ctg gaa cct ggg ctg agc tcc agt gct gcc tgt aat ggg aag  Ile Glu Leu Glu Pro Gly Leu Ser Ser Ala Ala Cys Asn Gly Lys  -15  -10  -5  1	3
gag atg tca cca acc agg caa ctc cgg agg tgc cct gga agt cat tgc 20 Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro Gly Ser His Cys 5 10 15	11
ctg aca ata act gat gtt ccc gtc act gtt tat gca aca acg aga aag Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala Thr Thr Arg Lys 20 25 30	; <b>9</b>
cca cct gca caa agc agc aag gaa atg cat cct aaa tagcaccatt 29 Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys 35 40 45	)5
aagtettttg teaaggtetg actaggteaa gggtaatgga eeagtateat etggtgatet 35 ggtaaacaaa taaaagtggt ggeacettea aaaaaaaaaa a 39	
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-20 -15 gtt etc tgt gtg etg etg eag gee eag gga gga tae egt gae aag	99
Val Leu Cys Val Leu Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys -10 -5 1 5	
atg agg atg cag aga atc aag gtc tgt gag aag cga ccc agc ata gat  Met Arg Met Gln Arg Ile Lys Val Cys Glu Lys Arg Pro Ser Ile Asp  10 15 20	47
	95
	40

tgagtgggag agtgggctgg gatgtgcatc ctgctccctg aaccettcca tccgagactg tgcccacatc cgaagcacaa ggacatcaaa tcatcagcac aagaacatca acaggaatgc caccetcccc agtgtctgaa ctccctgtcc ctgtcaaatg aaccagaaca aatgcccatg aaaaaaaaaa	300 360 420 432													
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aag ctg ttt gat gcc ccc ttg tcc atc agc aag aga gag cag ctg gaa Lys Leu Phe Asp Ala Pro Leu Ser Ile Ser Lys Arg Glu Gln Leu Glu 10 15 20	160													
cag cag gtc cca gag aac tac ttc tat gtg cca gac ctg ggc cag gtg Gln Gln Val Pro Glu Asn Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val 25 30 35 40	208													
cct gag att gat gtt cca tcc tac ctg cct gac ctg ccc ggc att gcc Pro Glu Ile Asp Val Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala 45 50 55	256													
aac gac ctc atg tac att gcc gac ctg ggc ccc ggc att gcc ccc tct Asn Asp Leu Met Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser 60 65 70	304													
gcc cct ggc acc att cca gaa ctg ccc acc ttc cac act gag gta gcc Ala Pro Gly Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala 75 80	352													
gag cct ctc aag acc tac aag atg ggg tac taacagcacc accaccgccc Glu Pro Leu Lys Thr Tyr Lys Met Gly Tyr 90 95	402													
CCaCCaaaaa aaaaaaaa	420													
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<223> Von Heijne matrix score 5.4

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ttg atc ttc ggt ctc gga gca gtt tgg ggg ctt ggt gtg gac cct tcc Leu Ile Phe Gly Leu Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser -10 -5 1 5	160
cta cag att gac gtc tta aca gag tta gaa ctt ggg gag tcc acg acc Leu Gln Ile Asp Val Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr 10 15 20	208
gga gtg cgt cag gtc ccg ggg ctg cat aat ggg acg aaa gcc ttt ctc Gly Val Arg Gln Val Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu 25 30 35	256
ttt caa gat act ccc aga agc ata aaa gca tcc act gct aca gct gaa Phe Gln Asp Thr Pro Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu 40 45 50	304
cag ttt ttt cag aag ctg aga aat aaa cat gaa ttt act att ttg gtg Gln Phe Phe Gln Lys Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val 55 60 65 70	352
acc cta aaa cag acc cac tta aat tca gga gtt att ctc tca att cac Thr Leu Lys Gln Thr His Leu Asn Ser Gly Val Ile Leu Ser Ile His 75 80 85	400
cac ttg gat cac agg taaatgtggt tgctggagtt tcctgtgttt tcattatatg His Leu Asp His Arg	455
90 tggttaaatg aatatattaa agagaagtaa acaaaaaaaa aaaaaa	501
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ttt tgt ctt aga tgt acg tac ttt cct gtt cat tgt ggt atg tgt aat Phe Cys Leu Arg Cys Thr Tyr Phe Pro Val His Cys Gly Met Cys Asn -35 -30 -25	220
ttg cgt tac ttt gaa ttt tcc acg ttt tta ctt tct ttg tct ctc atc Leu Arg Tyr Phe Glu Phe Ser Thr Phe Leu Leu Ser Leu Ser Leu Ile -20 -15 -10	268

Thr Tyr Cys Phe Trp Asp Pro Pro His Arg Gly Ser His Ser Leu Ser -5 1 10	316
cta gag cac act ccc ttg gat ttc ctc gag tgg ggt ctg ctg cgg Leu Glu His Thr Pro Leu Asp Phe Leu Glu Trp Gly Leu Leu Arg 15 20 25	361
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gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt Met Leu Phe Ser Leu Ser Leu -10	
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt Met Leu Phe Ser Leu Ser Leu -10 ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac	52 100
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac  Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5 1 5 10	
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac  Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5  1  5  10  att cct ggc caa tca gct cag ctg ttt att tac caa atg tct tca caa	
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac  Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5  1  5  10  att cct ggc caa tca gct cag ctg ttt att tac caa atg tct tca caa  Ile Pro Gly Gln Ser Ala Gln Leu Phe Ile Tyr Gln Met Ser Ser Gln	100
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac  Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5  1  5  10  att cct ggc caa tca gct cag ctg ttt att tac caa atg tct tca caa  Ile Pro Gly Gln Ser Ala Gln Leu Phe Ile Tyr Gln Met Ser Ser Gln  15  20  25	100 148
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5 1 5 10  att cct ggc caa tca gct cag ctg ttt att tac caa atg tct tca caa Ile Pro Gly Gln Ser Ala Gln Leu Phe Ile Tyr Gln Met Ser Ser Gln  15 20 25  caa cta cag cag cag cct tcg gct aac aaa aaa gca gga aaa atc cac	100
gtcaggttgc accgcccttt ggttcccgag c atg ctg ttt tct ctc agc ctt  Met Leu Phe Ser Leu Ser Leu  -10  ctc tcc aac ctt aac caa atc ggc agc agc cac ctc gac cgc cca cac  Leu Ser Asn Leu Asn Gln Ile Gly Ser Ser His Leu Asp Arg Pro His  -5  1  5  10  att cct ggc caa tca gct cag ctg ttt att tac caa atg tct tca caa  Ile Pro Gly Gln Ser Ala Gln Leu Phe Ile Tyr Gln Met Ser Ser Gln  15  20  25  caa cta cag cag cag cct tcg gct aac aaa aaa gca gga aaa atc cac  Gln Leu Gln Gln Gln Pro Ser Ala Asn Lys Lys Ala Gly Lys Ile His  30  35  40	100 148
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Ä.

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Signature   San Val   Ala His Gly   Leu Ala Try   Ser   Tyr   Ty			100					105					110			_		
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Tyr Leu Arg Leu IIe Leu Pro Glu Leu Gln Ala Arg Ile Arg Thr Tyr 130 aat cag cat tac aac aac ctg cta cgg ggt gca gtg agc cag cgg ctg 631 Asn Gln Ris Tyr Asn Asn Leu Leu Arg Gly Ala Val Scr Gln Arg Leu 150 150 150 155 160 160 160 160 160 165 170 175 165 160 160 160 165 170 175 165 165 170 175 165 165 170 175 165 165 170 175 165 165 170 175 171 le Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met 165 170 175 175 180 180 180 180 180 180 180 190 190 190 190 190 190 190 190 190 19	tat	ctg	cgg	ctg	atc	ctg	cca	gag	ctc	cag	gcc	cgg	att	cga	act	tac	583	3
aat cag cat tac aac aac ctg cta cgg ggt gca gtg agc agt gag cag cgg ctg         631           Asn Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln Arg Leu 150         160         165           tat att ctc ctc cca ttg gac tgt ggg ggg ggg cct gat acc ctg agt atg 167         165         160         165           Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met 165         170         175         175           gct gac ccc aac att cgc ttc ctg gat aac ctg ccc aac act cgc ctg gac acc gac acc acc acc acc acc acc ac	Tyr	Leu	Arg	Leu	Ile	Leu	Pro	Glu	Leu	Gln	Ala	Arg	Ile	Arg	Thr	Tyr		
Asn Gln His Tyr Asn Asn Leu Leu Arg Gly Ala Val Ser Gln Arg Leu  150  150  150  155  160  167  Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val Pro Asp Asn Leu Ser Met  165  165  170  175  Gct gac ccc aac att cgc ttc ctg gat aaa ctg ccc gag aac ggt 727  Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly  180  185  180  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  185  180  187  Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn Ser Ile Tyr Glu  195  200  ctt ctg gag aac ggg cag cgg ggc acc tg gtc ctg gag tac gcc  1823  Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr Cys Val Leu Glu Tyr Ala  210  215  220  225  226  225  226  227  227  228  228  228  229  230  240  121  230  235  240  241  245  250  240  245  246  247  248  248  249  248  249  240  241  241  250  255  240  241  242  242  243  244  245  246  247  248  249  249  249  240  241  241  242  243  244  245  246  247  248  249  248  249  249  249  240  241  241  242  242  243  244  244  245  246  247  248  249  248  249  249  249  240  241  240  241  241  242  242  243  244  245  246  247  248  248  249  249  249  249  240  241  241  242  243  244  245  246  247  248  248  249  249  249  249  240  241  241  242  243  244  245  246  247  248  248  249  248  249  249  249  249																		
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Second   S	•						р	C, D		VU.	110	Map	Maii		261	Mer		
Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys Leu Pro Gln Gln Thr Gly  180  180  180  185  186  187  188  188  189  180  180  188  382  382  382  383  384  387  381  381  381  381  382  383  383  383	gct	gac	ccc	aac	att	cgc	ttc	ctq		aaa	cta	ccc	caq		acc	aat.	727	7
180	Ala	Asp	Pro	Asn	Ile	Arg	Phe	Leu	Asp	Lys	Leu	Pro	Gln	Gln	Thr	Glv	,	
Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr Ser Asn Ser Ile Tyr Glu  195  ctt ctg gag aac ggg cag cgg ggc acc ttg tgc ctg gag tac gcc  205  ctt ctg gag aac ggg cag cgg ggc acc ttg tgc ctg gag tac gcc  215  220  225  226  227  228  229  225  220  225  220  225  226  227  227  228  229  227  228  229  227  228  229  229			180					185					190			-		
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aatcactgcc ttacctccct cacggttgtt gtgaggactg agtgtgtgga agtttttcat 1454	ttgg	gcca	gt c	attt	cccc	t ct	ctga	gcct	cgg	tgtc	ttc	aacc	tata	aa a	tage	atcat	1394	
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Ctt ccc aag cta tct tct tat tct gga tgg gta gag cac gtc cta Leu Pro Lys Leu Ser Ser Tyr Ser Gly Trp Val Val Glu His Val Leu  45  50  55	244													
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141.95

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cct	cac	ctg	aac	ctg	tgg	ctg	gaa	gcc	ccc	gac	ctc	ctc	ttg	gcc	gaa	852	2
Pro	His	Leu	Asn	Leu			Glu	Ala	Pro	Asp	Leu	Leu	Leu	Ala	Glu		
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Val	Asp	Leu	Pro			Asp	GIY	Ala			ьeu	ser	ьeu	220	Ile		
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Tyr G	ilv i	Leu	Cvs	His	Glv	Ser	Ala	Gly	Asn	Ala	Tyr	Ăla	Phe	Leu	Thr	
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+++	~~~	att	60	a > a	+-+	~~t	~~~	65					70	ggc		220
Phe	Asp	Val	Lvs	Glu	Tyr	yac Asn	Ara	yca Ma	gca Ala	vic	Dho	ctg	Cat	Gly	cyc	339
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Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser Asp Leu Lys Arg Ile Asn

Fà

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ccgac cccga gcc g Ala A tcg c Ser c gcc c Ala I agt g	ycg ggAla G	a gagga c atg d Met d gc ctt ly Leu ac aag sn Lys dag gca lu Ala ct gag er Glu	agcgc ctc g phe G ggg Gly -5 ggc Gly gca Ala	gaa g Glu G -20 ccc Pro tcc Ser tct Ser gag Glu 45	gag of the state o	atc Ile cgc Arg 15 tcc Ser gag Glu	tca Ser cgc Arg cag Gln gaa Glu	cga Arg l cag Gln cat His	ctc Leu ccc Pro aag Lys	ccg Pro ttg Leu ccc Pro 35 aag Lys	cct Pro gcc Ala 20 agc Ser aaa Lys	gcc of Ala I gcg Ala 5 aca Thr cta Leu tgc Cys	gcc Ala tta Leu tgt Cys	ta Val 10 tcc Ser cgg Arg ata Ile aaa Lys 55	109 157 205 253 301
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cccga cccga gcc g Ala A tcg g Ser G gcc G Ala I agt g Ser A agg g Lys A	y 107 cttcca gcg gg Ala G caa ac Gln A cta gc Leu G 25 gac t Asp S gca t Ala S	a gagga c atg c Met : gc ctt ly Leu ac aag sn Lys ag gca lu Ala ct gag er Glu ca ttt er Phe	agcgc ctc c phe C ggg Gly -5 ggc Gly gca Ala gag Glu gcc Ala 60 aaa	gaa	gag of slu I gta Val aag Lys ctt Leu 30 gag Glu gcc Ala	atc Ile atc Ile cgc Arg 15 tcc Ser gag Glu tct Ser cca	tca Ser cgc Arg Gln gaa Glu gct Ala	cga Arg l cag Gln cat His agg Arg gaa Glu 65	ctc Leu ccc Pro aag Lys 50 gta Val	ccg Pro ttg Leu ccc Pro 35 aag Lys ggg Gly	geg edla A cet Pro gec Ala 20 agc Ser aaa Lys aag	gcc G Ala I gcg Ala 5 aca Thr cta Leu tgc Cys aaa Lys	gcc Ala tta Leu tgt Cys ccc Pro 999 Gly 70 gaa	ta Val Val Val Val Val Val Val Val Val Va	109 157 205 253 301
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gcc call age	y 107 cttcca gcg gg Ala G caa ac Gln A cta gc Leu G gac t Asp S gac t Ala S gac t Ala S gac t Ala S	a gagga c atg Met : gc ctt ly Leu ac aag sn Lys ag gca lu Ala ct gag er Glu ca ttt er Phe gt caa ys Gln 75 gg aag rg Lys	ggg Gly -5 ggc Gly gca Ala gag Glu gcc Ala 60 aaa Lys	gaa	gag of slu I gta Val aag Lys ctt Leu 30 gag Glu gcc Ala ggc Cys	atc gc atc Ile cgc Arg 15 tcc Ser gag Glu tct Ser cca Pro cac His 95	tca Ser cgc Arg Gln gaa Glu gct Ala cct Pro 80 aaa Lys	cga Arg l cag Gln cat His agg Arg gaa Glu 65 tgc Cys cag Gln	ctc Leu ccc Pro aag Lys 50 gta Val agt Ser Ala	ccg Pro ttg Leu ccc Pro 35 aag Lys ggg Gly gac Asp	geg edla A cet Pro gec Ala 20 agc Ser aaa Lys tet Ser gtt Val 100	gcc G Ala I gcg Ala 5 aca Thr cta Leu tgc Cys aaa Lys Glu 85 ggc Gly	gcc Ala tta Leu tgt Cys ccc Pro ggg Gly 70 gaa Glu agt Ser	ta Val Val Val Val Val Val Val Val Val Va	109 157 205 253 301 349 397
cccga cccga gcc g Ala A tcg g Ser G gcc g Ala I agt g Ser A agg g Lys A gta g Val G	y 107 cttccc gcg gg Ala G cta gg Leu G cys to Asp S gca t Ala S gca t Ala S gca t Ala S gca t Ala S gca t G Asp S gca t G Asp S gca t G Asp S gca t G G Asp S gca t G G G G G G G G G G G G G G G G G G G	a gagga c atg Met : gc ctt ly Leu ac aag sn Lys ag gca lu Ala ct gag er Glu ca ttt er Phe gt caa ys Gln 75 gg aag rg Lys	agcgc ctc co che co ggg Gly -5 ggc Gly gca Ala gag Glu gcc Ala Lys aag Lys	gaa Glu Gloor Pro tcc Ser tct Ser gag Glu 45 agt Ser cag Gln aaa Lys aaa	gag of slu I gta Val aag Lys ctt Leu 30 gag Glu gcc Ala ggc Cys aga	atc gc atc Ile cgc Arg 15 tcc Ser gag Glu tct Ser cca Pro cac His 95 aag	tca Ser cgc Arg Cag Gln gaa Glu gct Ala cct Pro 80 aaa Lys	cga Arg l cag Gln cat His agg Arg Glu 65 tgc Cys cag Gln aaa	ctc Leu ccc Leu ccc Pro aag Lys 50 gta Val agt Ser Ala	gag Glu A ccg Pro ttg Leu ccc Pro 35 aag Lys Gly gac Asp ctt Leu cag	gcg cclar Pro gcc Ala 20 agc Ser aaa Lys tct Ser gtt Val 100 aaa	gcc Gly	gcc Ala tta Leu tgt Cys ccc Pro ggg Gly 70 gaa Glu agt Ser	ta Val 10 tcc Ser cgg Arg ata Ile aaa Lys 55 aag Lys gaa Glu gac Asp	109 157 205 253 301 349 397

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ata	aat	tca	gcc	cag	cac	ctg	gac	aat	gtt	gac	caa	aca	ggt	ccc	aaa	541
Ile	Asn	Ser	Ala	Gln		Leu	Asp	Asn	Val		Gln	Thr	Gly	Pro	Lys	
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ATO	TIP	Буз	GLY	140	1111	1111	71011	p	145		-1-			150	,	
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Ser	Thr	Ser	Pro	Lys	Pro	Pro	His		Leu	Ser	Arg	Lys		Trp	Arg	
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aac	cgg.	Caa	aag Lys	aat	aag	aga	aga	Cvs	Lvs	Asn	Lvs	Phe	Gln	Pro	Pro	
WPII	Arg	170	цуз	ASII	Lys	Arg	175	Cys	טעם		2,0	180				
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Gln	Val	Pro	Asp	Gln	Ala	Pro	Ala	Glu	Ala	Pro	Thr	Glu	Lys	Thr	Glu	
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Leu	Arg	Āla	Arg	Met	Ala	Gln	Arg	Leu	Asp	Gly	Ala	Arg	Phe	Arg	Tyr	
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Leu	Asn	GIU	Gln 235	ьeu	Tyr	Ser	GIA	240	ser	ser	Ala	Ald	245	Arg	neu	
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Phe	Gln	Glu	Asp	Pro	Glu	Ala	Phe	Leu	Leu	Tyr	His	Arg	Gly	Phe	Gln	
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Val	Pro		Glu	Asp	Glu	Ser			Val	Ala	Val			Leu	Ser	
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360		~	cga		365			act	ata	370		cta	aac	ttc		1309
Glu	Asp	Val	Arg	Thr	Phe	Leu	Aro	Ala	Val	Thr	Lys	Leu	Gly	Phe	Lys	
-	,,,,,,		•	380					385				•	390		
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Ile	Val	Ser	Lys		Leu	Thr	Asn			Phe	Phe	Leu			Phe	
			395					400		220	act		405		aac	1405
Gla	Lag	Thr	- 61v	Pro	Pro	Leu	Val	Glv	Pro	Lvs	Ala	Gln	Leu	Ser	ggc	1100
011		410	_			u	415			-,-		420			. = 3	
		ctt	cag									ccto	tgg	atct	tccttg	1458
	Gln	Lev	Gln			Leu	Туг									
	425					430			<b>~</b> ~				.+++		ectess	1518
aga	9999	agg	caga	tacto	aa a	CTCC	aggo	ic ca	gaac	cgtg	aag	atas	taa	aacc	cctggc tctggc	1578
Lyt	.yagc	cad	yacc	·-yyt	(	، دین د	.yyal		9099	acad	agt	2-20			22-330	

rig Figs

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-84-

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··<220>

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<223> Von Heijne matrix
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<222> 793..805

<400> 110

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score 4.1

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Ser Ser Pro	Ser Leu Lys Thr	Asp Thr Ser	Pro Val Leu	Glu. Thr Ala	
-45	-40		-35	-30	
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Gly Thr Val	Ala Ala Met Ala				
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5	. 10		15	aat cog ttg 292	
gtg cac aag	ccc aaa ggg ccc	act tca gc	gag ctg ctg		
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20	25		30		
aag gag aag	ctg ctg gca gaa	get gga at	Tro for Dro	Jan - 23	
ras Gin ras	Leu Leu Ala Glu	Ala Gly Mei	Pro ser Pro	50	
	40 aag cag act ttg		r cat daa daa	=	ł
	Lys Gln Thr Leu				
nys arg nys	55	60	, mis dry dry	65	
200 002 000	cga gga gtt ctg		a att oga agc		;
	Arg Gly Val Leu				
70	mry dry var neu	75	80	-3-	
	agt atg ttg tca	. •		gcc att gga 484	Į
	Ser Met Leu Ser				
85	90	,,	95	-	
	aaa gct act gat	aca cta qa	t tot acq qqq	aag gta aca 532	!
Glu Leu Gly	Lys Ala Thr Asp	Thr Leu As	o Ser Thr Gly	Lys Val Thr	
100	105		110	115	
	cct tac ggt atg	aac ctc at	c taagtag	569	)
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ct	g	ctt	gaa	gag	ctt	CCC	ctc	ccc	gac	cag	cag	CCa D	tgc	Tla	Glu	Dro	,,,
Le	u	Leu		Glu	Leu	Pro	Leu		Asp	GIN	GIN	Pro	Cys	TIE	Gru	PLO	
			-75					-70	~~+		+++	<b>~</b>		aac.	+++	gag	144
CC	:a	cct	tcc	tcc	atc	atg	tac	cag	gct	Aac	Dha	Acn	aca	Asn	Phe	Glu	
Pr			Ser	ser	TIE	Met	-55	GIII	ATa	ASII	FILE	-50	Thr	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
	_	-60		~~~		ata		aac	att	aca	add		att	gag	caq	qct	192
ga	IC	agg	Aar Aar	yca Nla	Dhe	Val	Thr	GJV	Tle	Ala	Ara	Tvr	Ile	Glu	Gln	Ala	
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		atc	cac	téc	age		aat	qaq	atq	ctq	qaq	gaa	gga	cat	gag	tat	240
ጥት	.a	Val	His	Ser	Ser	Met	Asn	Glu	Met	Leu	Glu	Glu	Gly	His	Glu	Tyr	
. 4.1	· ·	• • • •			-25					-20					-15		
ac	a	atc	atq	ctq	tac	acc	tgg	cgc	agc	tgt	tcc	cgg	gcc	att	ccc	cag	288
A)	la	Val	Met	Leu	Tyr	Thr	Trp	Arg	Ser	Cys	Ser	Arg	Ala	Ile	Pro	Gln	
				-10					-5					1			
at	ca.	aaa	tgc	aac	gag	cag	CCC	aac	cga	gta	gag	atc	tat	gag	aag	aca	336
٧a	al	Lys	Cys	Asn	Glu	Gln	Pro	Asn	Arg	Val	Glu	Ile	Tyr	Glu	Lys	Thr	
		5					10					15			•		204
gt	ta	gag	gtg	ctg	gag	ccg	gag	gtc	acc	aag	ctc	atg	aag	ttc	atg	tat	384
Vá	al	Glu	Val	Leu	Glu	Pro	Glu	Val	Thr	Lys	Leu	Met	Lys	Pne	met	Tyr	
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ti	tt	cag	cgc	aag	gcc	atc	gag	cgg	ttc	tgc	agc	gag	gtg	aag	250	Len	752
P	he	Gln	Arg	Lys		Ile	Glu	Arg	Pne		ser	GIU	Val	гуу	50	пец	
					40					45	+a+		acc	tac		cta	480
t	gc	cat	gcc	gag	cgc	agg	aag	gac	Dhe	y.c	Cor	Glu	gcc Ala	Tvr	Leu	Leu	
C.	ys	His	Ala		Arg	Arg	ьys	Asp	60	vaı	561	OI u	7124	65			
-		att	~~~	55	++~	atc	aac	atα		act	atc	cta	gat		cta	aag	528
et.	CC hr	Len	Gly	Live	Dhe	Tle	Asn	Met	Phe	Ala	Val	Leu	Asp	Glu	Leu	Lys	
1.	111	шеα	70	Бys	FIIC		*****	75		•			80				
а	ac	atq	aad	tac	ago	atc	aaq	aat	gac	cac	tcc	gcc	tac	aag	agg	gca .	576
A	sn	Met	Lys	Cys	Ser	Val	Lys	Asn	Asp	His	Ser	Ala	Tyr	Lys	Arg	Ala	
		85					90					95					
g	ca	cag	tto	ctg	cgg	aag	atg	gca	gat	ccc	cag	tct	atc	cag	gag	tcg	624
Ā	la	Gln	Phe	Leu	Arg	Lys	Met	Ala	Asp	Pro	Gln	Ser	Ile	Gln	Glu	Ser	
1	00					105	,				110					112	622
С	ag	aac	ctt	tcc	atg	tto	ctg	gcc	aac	cac	aac	agg	ato	acc	cag	tgt	672
G	ln	Asn	Lev	Ser	Met	: Phe	Leu	Ala	Asn			Arg	11e	Thr	120	Cys	
					120	)				125					130		720
C	tc	cac	cag	caa	ctt	: gaa	gtg	ato	: cca	ggc	tat	gag	gag	Lev	Let	gct Ala	,20
:L	eu	His	Glr			ı Glu	val	. 116	140		туг	GIL	GIU	145	: Det	ı Ala	
				135												ctg	768
9	ac	act	gto	aac	ato	tgt	. g	) yat	. במנ י שיי	. cat	. gay	Δαι Δαι	. Lvs	Met	TVI	Leu	
A	sp	TTE	: va:		1 116	e Cys	, val	155		,.	. 010		160	)			
-	. ~+		150			- cat	ato			: aac	ata	aaa	cto		:		810
· т	'h~	Pro	. ayı	י פאני ר פאי	, aac	a His	Met	Let	ı Leı	ı Lys	Val	Lys	Lev	Pro	)		
•		165			- <i></i> , .		170			-4		175	5				
t	.ga	aaca	gca	CCC	itaa	agc (			ac co	etete	cacct	tct	tctt	att	aaaa	aatccgt	870
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Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val Asp
                                            -10
                        -15
    -20
ggg cta gtg cga agc agc ccc tcg ctg gac cag atg ttc gac gcc gag
                                                                     153
Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu
                    1
                                    5
-5
                                                                     201
atc ctg ggc ttt tcc acc cct cca ggc cgg ctc tcc atg atg tcc ttc
Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe
                                20
atc ttc aac gcc ctc acc tgt gcc ctg ggc ttg ctg tac ttc atc cgg
                                                                     249
Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg
                                                40
                            35
cga gga aag cag tgt ctg gat ttc act gtc act gtc cat ttc ttt cac
                                                                     297
Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His
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ctc ctg ggc tgc tgg ttc tac agc tcc cgt ttc ccc tcg gcg ctg acc
                                                                     345
Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr
                                        70
                    65
tgg tgg ctg gtc caa gcc gtg tgc att gca ctc atg gct gtc atc ggg
                                                                     393
Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly
                                    85
                80
gag tac ctg tgc atg cgg acg gag ctc aag gag ata ccc ctc aac tca
                                                                     441
Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn Ser
                                100
                                                                     489
gcc cct aaa tcc aat gtc tagaatcagg ccctttggac atcccgctga
Ala Pro Lys Ser Asn Val
        110
cacttgggcc ccttaacacc ttgggctgct cagaccctcc agatgaggtc cagcccagat
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ctgagaggaa ccctggaaat gtgaagtctc tgttggtgtg ggagagatag tgagggcctg
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ccttggtatc tgagaggtca ggaaggggac ctctttgagg gtaataacat aattggaacc
                                                                     729
                                                                     789
 atgccactct tgagccacaa tacctgtcac cagcctgttg tittaagaga gaaaaaaaat
                                                                      849
 caaggatate tgattggage aaaccactte tttagteate tgtettaeet eeetgggaca
                                                                      909
 gctgttacct ttgcagtgtt gccgaatcac agcagttacc tttgcaatgt tgccgaatca
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 taggacccag agaagaatcc cagtgttgct caaagtctga ccatcataaa gacactgcct
                                                                     1209
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                                                                     1269
 atttagaatt ctttggcggg aagggtatga tgggttccca gagacaagaa gcccaacctt
                                                                     1329
                                                                     1389
 ctggcctggg ctgtgctgat agtgctgagg gagataggaa tttgctgcta agatttttct
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.

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ttggggtgga gtttcctctg tgaggggctt gcagctatcc ttcctgtgta tacaaataca
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                                                                     1475
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gtg cag ccg aaa ata aaa cat cgc ccc ttc tgc ttc agt gtg aaa ggc
                                                                       104
Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser Val Lys Gly
                                         -25
                     -30
-35
                                                                       152
cac gtg aag atg ctg cgg ctg gtg ttt gca ctt gtg aca gca gta tgc
His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr Ala Val Cys
                                     -10
                 -15
tgt ctt gcc gac ggg gcc ctt att tac cgg aag ctt ctg ttc aat ccc
                                                                       200
 Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn Pro
 aac ggt cct tac cag aaa aag cct gtg cat gaa aaa aaa gaa gtt ttg
                                                                       248
Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu
                                             25
                         20
                                                                       308
 tgattttata ttacttttta gtttgatact aagtattaaa catatttctg tattcttcca
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 aaaaaaaaa aaa ·
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agg aga cag agg ctg gcc gag ctg cag gcc aaa cac ggg gat cct ggt Arg Arg Gln Arg Leu Ala Glu Leu Gln Ala Lys His Gly Asp Pro Gly -45 -40 -35 -30	99
gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aac Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn -25 -20 -15	147
agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta agt Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Ser -10 -5	195
aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat tac Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr 5 10 15	243
ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu 20 25 30 35	291
caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aag Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys 40 45 50	339
aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat gaa Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Glu 55 60 65	387
gat gac gat tat tgaactacaa gtgctcacag actagaactt aacggaacaa Asp Asp Asp Tyr	439
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ccg ccg cca ccc ctg tat acc cgg cac cgc atg ctc ggt cca gag tcc Pro Pro Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser	99
gtc ccg ccc cca aaa cga tcc cgc agc aaa ctc atg gca ccg ccc cga Val Pro Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg 10 15 20 25	147

e-: .

•	•															
atc Ile	Gly 999	acg Thr	cac His	aat Asn	ggc Gly	acc Thr	ttc Phe	cac His	tgc Cys 35	gac Asp	gag Glu	gca Ala	ctg Leu	gca Ala 40	tgc Cys	<b>195</b> .
gca Ala	ctg Leu	ctt Leu	cgc Arg	30 ctc Leu	ctg Leu	ccg Pro	gag Glu	Tyr	cgg	gat Asp	gca Ala	gag Glu	IIe	gtg	cgg Arg	243
acc Thr	cgg Arg	gat Asp	45 ccc Pro	gaa Glu	aaa Lys	ctc Leu	gct Ala	50 tcc Ser	tgt Cys	gac Asp	atc Ile	Val	55 gtg Val	gac Asp	gtg Val	291
aaa	aac	60 gag	tac	gac Asp	cct	cgg	65 aga	cac	cga	tat	gac	70 cat	cac	cag	agg .	339
	75			acc		80					85					387
Ser	Phe	Thr	Glu	Thr	Met 95	Ser	Ser	Leu	Ser	Pro 100	Gly	Arg	Pro	Trp	105	425
acc Thr	aag Lys	ctg Leu	agc Ser	agt Ser 110	gcg Ala	gga Gly	ctc Leu	atc Ile	tat Tyr 115	ctg Leu	cac His	ttc Phe	Gly 999	His 120	aag Lys	435
ctg Leu	ctg Leu	gcc Ala	cag Gln 125	ttg Leu	ctg Leu	ggc Gly	act Thr	agt Ser 130	gaa	gag Glu	gac Asp	agc Ser	atg Met 135	gtg Val	ggc Gly	483
acc Thr	ctc Leu	tat Tyr 140	gac Asp	aag Lys	atg Met	tat Tyr	gag Glu 145	aac	ttt Phe	gtg Val	gag Glu	gag Glu 150	gtg Val	gat Asp	gct Ala	531
gtg Val	Asp	aat	aaa	atc Ile	tcc Ser	cag Gln 160	tgg	gca Ala	gag Glu	ggg ggg	gag Glu 165	Pro	cga Arg	tat Tyr	gca Ala	579
Leu	Thr	act Thr	acc Thr	ctg Leu	Ser	qca	cga Arg	gtt Val	gct Ala	Arg	ctt Leu	aat	cct Pro	acc Thr	tgg Trp 185	627
170 aac Asn	cac	ccc	gac Asp	caa Gln	175 gac Asp	act Thr	gag Glu	gca Ala	Gly	Phe	aag	cgt Arg	gca Ala	Met	gat Asp	675
ctg Leu	gtt Val	caa Glm	gag Glu	190 gag Glu	ttt	ctg Leu	cag Gln	Arg	Leu	gat	tto Phe	tac Tyr	GID	His		723
tgg Trp	ctg Leu	cca	205 gcc Ala	caa	gcc Ala	ttg Leu	gtg Val	210 gaa Glu	gag	gcc Ala	ctt Lei	ı Ala	GIn	cga	ttc Phe	771
cag Gln	gtg Val	220 gao	. cca	agt Ser	gga Gly	gag Glu	225 att	gtg	gaa Glu	cto Lev	g gcg	230 g aaa a Lys	ggt	gca Ala	tgt Cys	819
ccc	235 tac	i Laac	a aac	cat	cto	240 tac	cac	cto	gaa	ı tct	245 gg:	s g ctg	tco	cct	cca	867
250 ato	acc	: ato	: ttc	: ttt	255 att	ato	tac	act	: gad	260 cag	) g gct	t gga	a cag	g tgg	265 g cga	915
				270	)				275	5				280		963
Ile	e Glr	з Су	s Val 285	l Pro	Lys	s Glu	Pro	His 290	s Sei )	r Phe	e Gl	n Sei	295	у ьег 5	g ccc 1 Pro	
Cto Let	g cca	a gag o Gl	u Pro	tgo Trp	o Arg	g ggt g Gly	ctt Let 30!	u Arg	g gad g Asj	gaç o Gli	g gc	c cto a Lei 310	ı Ası	c cag	g gtc n Val	1011
agt Se:	c Gly	g at	c cct	ggo Gly	tgo Cys	ato 320	tte Phe	c gto	c cat	t gc	a ag a Se 32	c gg r Gl	c tto	e att	ggc Gly	1059
Gl	y Hi	c cq	c acc	c cga r Arg	g Glı	g ggt u Gly	gc	c ttg a Le	g ag u Se	r Me	g gc t Al	c cg	t gc	c ace a Th	ttg Leu 345	1107
33 gc Al	c ca	g c <b>g</b> n Ar	c tc g Se	a tac r Ty:	33! c cto r Le	c cca	a ca o Gl	a at	c tc e Se	34 c ta r		aata	aaa	cctt		1157

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350

355

1173

686

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tcc cac tcc agg ctg tcc ccc cga aag acc cac tta ctg tac atc ctc

			•													
Ser H				:	165					170				Ile	Leu 175	734
agg ( Arg l	ecc tero	ct o	Arg (	cag ( Gln 1 180	ctg Leu	tagg	ggtg	gg g	accg	ggga	g ca	cctg	cctg			734
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		_									•					
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						~~+	~~~	gat	aca	at a	gaa	-60	cag	agg	caa	103
tgc Cvs	Cvs	aaa Lvs	Glv	Glv	Pro	Asp	Glu	Asp	Ala	Val	Glu	Arg	Gln	Arg	Arg	
	-55					-50					-45					151
cag	aag	ttg	ctt	ctt	gca	caa	ctg	cat His	Cac	aga	Lvs	agg	Val	Lvs	Ala	131
-40					-35					-30					-25	
act	<b>ggg</b>	cag	atc	cag	gcc	tgg	tgg	cgt	999	gtc	ctg	gtg	cgc	agg	acc	199
Ala	Gly	Gln	Ile	Gln -20	Ala	Trp	Trp	Arg	-15	Val	тел	vaı	Arg	-10	IIII	
ctq	ctg	gtt	gct	qcc	ctc	agg	gcc	tgg	atg	att	cag	tgc	tgg	tgg	agg	247
Leu	Leu	Val	Ala	Ala	Leu	Arg	Ala	Trp	Met	Ile	Gln	Cys 5	Trp	Trp	Arg	
aca	tta	ata	-5	aga	caa	atc	cat	1 cag	cqq	cqq	cag	-	ctg	ttg	agg	295
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gtc	Tyr	gtc Val	atc	Gln	gag Glu	Gln	Ala	acg Thr	Val	Lys	Leu	Gln	Ser	Cys	Ile	
25					30					35					40	
cgc	atg	tgg	cag	tgc	cgg	caa	tgt	tac	cgc	caa	atg	tgc	aat	gct	ctc	391
Arg	Met	Trp	Gin	Cys 45	Arg	GIN	Cys	туг	50	GIII	Met	Cys	ASII	55	Leu	
tgc	ttg	ttc	cag	atc	cca	gag	ago	agc	ctt	gcc	ttc	cag	act	gat	ggc	439
Cys	Leu	Phe	Gln	Val	Pro	Glu	Ser	Ser	Leu	Ala	Phe	Gln	Thr 70	Asp	Gly	
+++	tta	cag	60 atc	caa	tat	aca	ato	65 cct	tca	aag	cag	сса		ttc	cac	487
Phe	Leu	Gln	Val	Gln	Tyr	Āla	Ile	Pro	Ser	Lys	Gln	Pro	Glu	Phe	His	
		75					80					85				535
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PCT/IB98/02122 -

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aat gat too cag oto toa goo tog ttt otg caa coo ago otg caa goa
Asn Asp Ser Gln Leu Ser Ala Ser Phe Leu Gln Pro Ser Leu Gln Ala
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            -30
aac tgt cct gct ttg gac cct gct gtg tca ctc tcc gca cca gcc ttt
                                                                       147
Asn Cys Pro Ala Leu Asp Pro Ala Val Ser Leu Ser Ala Pro Ala Phe
                             -10
ged tet get ett ege tet atg aag tee tee cag get gea egg aag gac
                                                                       195
Ala Ser Ala Leu Arg Ser Met Lys Ser Ser Gln Ala Ala Arg Lys Asp
                                         10
 gac ttt ctc agg tct ctt agt gat gga gac tca ggg aca tca gaa cac
                                                                       243
Asp Phe Leu Arg Ser Leu Ser Asp Gly Asp Ser Gly Thr Ser Glu His
                                     25
 atc tca gcg gtg gtg act agc cct cgg att tcc tgc cat ggt gct gcc
                                                                       291
 Ile Ser Ala Val Val Thr Ser Pro Arg Ile Ser Cys His Gly Ala Ala
                                 40
             35
 att ccc acc gcc cgt gcc ctc tgc cta ggc tgt tcc tgc tgc acc gaa
                                                                       339
 Ile Pro Thr Ala Arg Ala Leu Cys Leu Gly Cys Ser Cys Cys Thr Glu
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 Arg Leu Leu Pro Pro Pro Ser Leu Leu Ser Leu Glu Ala Pro Ala
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 age ace tgagetetet getgattget \gtteeteeca gtetgtggaa getttgeeca
                                                                       443
 Ser Thr
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PCT/IB98/02122 ·

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His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Ala Phe Phe Ser  225 230 235	
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Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly	
240 245 250	
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Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala	
255 260 265	
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	202
Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr	
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Glu Pro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu	
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Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu	
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Val Gln Arg Lys Leu Asp Gln Lys Thr Lys	
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Met Asp Ash Arg Phe His Arg   Ash Arg Phe His Arg   Ash Arg Phe   Arg   Ash Arg Phe   Arg   Ash Arg   As	2400	anta	םם כ	aaac	agto	t da	atac	caqa	atq	gat	aac	cgt	ttt	gct	aca	gca	.54
The Note	ggag	yacy	99 0	guge	4900	· 5-			Met	Asp	Asn	Arg	Phe	Ala	Thr	Ala	
The time of the content of the con												_					
Phe Val Ile Ala Cys Val Leu Ser Leu Ile Ser Thi Ile Ile Ala Cys Val Leu Ser Leu Ile Ser Thi Ile Ile Ala Cys Ala Cys Val Leu Ser Leu Ile Ser Thi Ile Ile Ala Cys Ala Cas		~+ ^	-++	act	tat	ata	ctt	age			tcc	acc	atc	tac	atg	gca	102
The color of the	בבכ	gta	<b>a</b> ll	33-	Cyc.	77-1	LAN	Ser	Len	Tle	Ser	Thr	Ile	Tyr	Met	Ala	
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Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35  gat gaa gat gaa aag act tat aat gat gat gaa cct ttt cga tac aat 246  Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn Asp Gly Thr Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met 55 60  cat tgg tat agc cca cca gaa agg ac gg tgt atc acc ata ccc aaa aac atg 294  Gly Thr Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met 55 60  cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gt aca aca ttg gtg agt ttc aca cat act gag cag ttc atg gtg gtg gtc aca atg tgg gat ttc aca cta tgg tat gag atg ttc aca cta act gag cag ttc atg gtg gtg gtc aca aca tgg gtg gtg gtg gtc aca ttg gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt gtg lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val BS 90 90  gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt and Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu 105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc 486  cca cac att gcc gag ctt tgg cga ctt tgc gct tgc att tgc cga agc tta tat phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr 135 140  ccc acc att gcc acg gccattgg ggttcctgt gtagatgct cagctgaat cccaact tctttgga gccaccaact acacaact accaact accaact ccc accaccaact accacaact accaccaact accaccaact accaccaact accaccaact accaccaccaact accaccaact accaccaact accaccaact accaccaact accaccaccaccaccaccaccaccaccaccaccaccacc			-10							<b></b>	+ - +	cas	ant	cca	att	caa	150
5         10         15         20         198         198         198         198         60u Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198	gcc	tcc	att	ggc	aca	gac	ttc	tgg	cat	gaa	The second	25a	Cor	Dro	Val	Gln	
5         10         10         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         198         182         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192         192	Ala	Ser	Ile	Gly	Thr	Asp	Phe	Trp	Tyr	GIU	Tyr	Arg	261	FIU	Val	20	
gaa         aat         tca         asp         Leu         Asp         Lys         Ser         Ile         Trp         Asp         Glu         Phe         Ile         Ser         Ser         Japa	5														~++		198
Ser   Ser   Asp   Leu   Asp   Leu   Asp   Ser   The   Trp   Asp   Giu   Phe   Phe   Asp   Giu   Phe   Asp   Giu   Phe   Asp   Giu   Phe   Asp   Giu   Asp   Giu   Lys   Thr   Tyr   Asp   Asp   Asp   Giu   Lys   Thr   Tyr   Asp   Asp   Ala   Pro   Phe   Arg   Tyr   Asp   Asp   Giu   Trp   Asp   Asp   Asp   Ala   Pro   Phe   Arg   Tyr   Asp   Asp   Giv   Thr   Val   Giv   Leu   Trp   Arg   Arg   Cys   Thr   Tile   Pro   Lys   Asp   Met   Ser   Cos   Cas   Gas   asg   aca   aca   aca	gaa	aat	tcc	agt	gat	ttg	aat	aaa	agc	atc	tgg	gat	gaa	TTC	#11-	age	170
gat gaa gca gat gaa aag act tat aat gat gca cct ttt cga tac aat 246 Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn  40	Glu	Asn	Ser	Ser	Asp	Leu	Asn	Lys	Ser	Ile	Trp	Asp	GIu	Pne	116	Ser	
gat gaa gaa gaa gaa gac tat gab aag act tat alt gat gab       gat gaa gaa gaa gac tat gab aag act tat alt gat gab       gat gab gab       gab aag cab       gab aag act gab       gab aag act gab       gab aag act gab       gab aag acg       gab acg					25					30					35		
Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Pine Atl Tyr Asn Met Asp Ala Pro Pine Asp Ala Pro Lys Asn Met Asp Ala Pro Pine Asp Ala Pro Lys Asn Met Asp Ala Lys Cys Pine Asp Val Val Thr Asp Asp Ala Cys Ile Asp Leu Leu Arg Thr Tyr Leu Ala Pine Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu Ala Pro Pine Asp Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr Asn Asp Ala Pro Pine Atl Cys Ile Cys Arg Ser Leu Tyr Asn Asp Ala Pro Pine Asp Ala Cys Ile Cys Arg Ser Leu Tyr Asp Cys Caca att gca acg att cat cat cat cat asp Ala Pro Pine Asp Cala Pro Pine Asp Ala Asp Pro Pine Asp Ala Cys Ile Cys Arg Ser Leu Tyr Asn Caca acc att gca acg act tat cat acc acc acc acc acc acc acc	gat	gaa	αca	gat	qaa	aaq	act	tat	aat	gat	gca	cct	ttt	cga	tac	aat	246
ggc aca gtg gga ttg tgg aga cgg tgt atc acc ata cca ac act act ggc tgt atc acc ata ccc aca act act ggc tgt atc acc ata ccc act act act ggt tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca act ggt gtg atc act ggt gtg agt tca cca act gac gag cag ttc att gat gtg gtc aca act ggt gtg agt ttc aca cta act gag cag ttc atg gag aca ttt gtt gtg gtc aca act ggt gtg gtc aca act gtg gtg gtc act gtg gtg gtg gtg gtg gtg gtg gtg gtg g	yen	Glu	Ala	Asp	Ğlu	Lvs	Thr	Tyr	Asn	Asp	Ala	Pro	Phe	Arg	Tyr	Asn	
ggc aca         gtg gga ttg tgg aga cgg tgt atc acc ata ccc aaa aac atg         294           Gly Thr         Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met         55           cat tgg tat agc cca cca gaa agg aca agg tca ttg gt gt gtc aca         342           His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr         70           aaa tgt gtg agt ttc aca cta act gag gag cag ttc atg gag aaa ttt gtt         390           Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val         390           gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt         438           Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu         110           tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta gg tttg atg tgc         486           Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys         125           120         125         130           ttt ggg gct ttg atc gac ctt tgt gct tgc att tgc ga agc tta tat tgc ga agc tta tat         534           Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr         135           ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg         534           Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu         160           tgaagtccag gccacatgga ggctcctgt gtagagtctc ggcagtcatc tctggagtgtcat accatcattaa agaactaac accatcattaa agaactaaccataaccatcatcaaccataaccatcaaccaaccaaccaaccaaccaaccaaccaaccaaccaaccaaccaaccaaccaaccaa				40					45					50			
Cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca   342	~~~	202	ata	aaa	tta	taa	aga	caa	tat	atc	acc	ata	ccc	aaa	aac	atg	294
Cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca  His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr  70 75 80  aaa tgt gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt  Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val  85 90 95 100  gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt  Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu  105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135 140 145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc  gcattaacaa gccttcagag gacttcagcc acagctatta tcgaactga tggagccatc tggaggcaac acc acc acc acc acc acc acc ac	gge	mb	919	994	Tou	Trn	720	Ara	Cvs	Tle	Thr	Ile	Pro	Lys	Asn	Met	
Cat tgg tat agc cca cca gaa agg aca gag tca ttt gat gtg gtc aca  His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr  70	GIY	Int		GIY	Dea	пр	nr9		O, D				65	•			•
His Trp Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Im			55				~~~		202	727	tca	ttt		ata	atc	aca	342
70       75       80         aaa tgt gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt       390         Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val       100         gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt       438         Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu       105         tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc       486         Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys       120         ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat       130         ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat       534         Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr       135         ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg       582         Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu       150         tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gcctcaact gacagcaac atcattcca gccatgtgtg ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc accatgaccac tcctagcaact tccttgtgag actctaataa agaaccaact agctgagccc accatgaccact tggaactacaact tccttgtgag actctaataa agaaccaact agctgagccc accatgaccact tggaactacaact tccttgtgag actctaataa agaaccaact agctgagccc	cat	tgg	tat	agc	cca	cca	gaa	agg	mbs	gay	Cor	Dhe	yen	Val	Val	Thr	
aaa tgt gtg agt ttc aca cta act gag cag ttc atg gag aaa ttt gtt  Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val  85 90 95 100  gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt  Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu  105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135 140 145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc acceptaa gccttcaaca gccttcaaca gccttcaaca acceptaa ac	His		Tyr	Ser	Pro	Pro		Arg	Int	GIU	Ser	5110	Asp	Vul	***		
Lys Cys Val Ser Phe Thr Leu Thr Glu Gln Phe Met Glu Lys Phe Val  85 90 95 100  gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt  Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu  105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135 140 145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gcctcaaca gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822  actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822		70													+++	att	390
gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr  105  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  110  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  120  125  120  125  130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135  140  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc gcctcaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822  822  822	aaa	tgt	gtg	agt	ttc	aca	cta	act	gag	cag	TTC	atg	gag	daa	Dho	yet vel	550
gat ccc gga aac cac aat agc ggg att gat ctc ctt agg acc tat ctt  Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu  105 110  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120  125  130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135  140  150  150  150  150  155  160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc gcctcaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822  822	Lys	Cys	Val	Ser	Phe	Thr	Leu	Thr	Glu	Gln	Phe	Met	GIU	гàг	Pne	val	
Asp Pro Gly Asn His Asn Ser Gly He Asp Leu Leu Arg Hi Tyl Beu 105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc 486  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys 120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr 135 140 145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu 150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822	85	_				90										-	420
Asp Pro Gly Asn His Asn Ser Gly He Asp Leu Leu Arg Hi Tyl Beu 105 110 115  tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc 486  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys 120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr 135 140 145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu 150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822	gat	ccc	qqa	aac	cac	aat	agc	999	att	gat	ctc	ctt	agg	acc	tat	Ctt	438
tgg cgt tgc cag ttc ctt tta cct ttt gtg agt tta ggt ttg atg tgc  Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120  125  130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135  140  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822  822	Asp	Pro	Glv	Asn	His	Asn	Ser	Gly	Ile	Asp	Leu	Leu	Arg	Thr	Tyr	Leu	
Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135 140  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822					105					110					TT2		
Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser Leu Gly Leu Met Cys  120 125 130  ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135 140  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822	taa	cat	tac	сад	ttc	ctt	tta	cct	ttt	gtg	agt	tta	ggt	ttg	atg	tgc	486
ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135  140  145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822  262	£22	720	Cve	Gln	Dhe	Leu	Leu	Pro	Phe	Val	Ser	Leu	Gly	Leu	Met	Cys	
ttt ggg gct ttg atc gga ctt tgt gct tgc att tgc cga agc tta tat  Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr  135  140  145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822	тър	nr 9	Cyb						125					130			
Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyt  135  140  145  ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctcccaact gacagccaac atcattcca gccatgtgt ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822		~~~	act	++0	atc	ada	ctt	tat	act	tac	att	tqc	cga	agc	tta	tat	534
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ccc acc att gcc acg ggc att ctc cat ctc ctt gca gat acc atg ctg  Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150  155  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctcccaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa  822	Pne	GIY			116	GIY	пси	140	7124	٠, ٠		-1	145			_	
Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala Asp Thr Met Leu  150 155 160  tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa gctcccaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822			135							ata	ctt	aca	gat	acc	atq	cta	582
tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa 642 gctcccaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca 702 gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag 762 actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822	ccc	acc	att	gcc	acg	ggc	all	Ton	Tida	Ton	LOU	Δla	) Den	Thr	Met	Leu	
tgaagtccag gccacatgga ggtgtcctgt gtagatgctc cagctgaaat cccaagctaa 642 gctcccaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca 702 gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag 762 actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822	Pro			Ala	Thr	GIA	116	Leu	urs	пеп	Leu	160	, ASP				
gctccaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca 702 gcctcaact gacagccaac atcatttcca gccatgtgtg ggagccatcc tggatgtcca 762 gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttgtgag 762 actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822		150					155			- 4				t	0000	acctaa	642
gctcccaact gacagccaac atcatttcca gccatgtyty ggagccatco tygatgood 762 gccttaacaa gccttcagag gacttcagcc acagctatta tcttactaca tccttytgag 762 actctaataa agaaccaact agctgagccc aatcaaccta tggaactgat agaaataaaa 822	tga	agto	cag	gcca	cate	ıga g	gtgt	.cctg	it gt	agat	gctc	cag	lerda	laat		tataa	
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								act Thr								70
-10	ьеu	Gry	Бец	Met	-5	VAI	vaı	1111	Gry	1	Gru	Asp	GIU	5	501	
	tat	acc	cat	gag	_	ctc	cta	gac	gag	_	acc	ctc	ttt	tac	caq	146
								Asp								
	_		10					15		-			20	•		
ggc	ctt	gaa	gtt	ttc	tac	cca	gag	ttg	999	aac	att	ggc	tgc	aag	gtt	194
Gly	Leu	Glu	Val	Phe	Tyr	Pro	Glu	Leu	Gly	Asn	Ile	Gly	Cys	Lys	Val	
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_		_	•				_	cag	_					-	_	242
Val		Asp	Cys	Asn	Asn	-	Arg	Gln	ràs	He		Ser	Trp	Met	Glu	
	40					45		~ + ~			50				a+~	290
								gtg Val								290
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								Asp								
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Lys	Gly	-	Ile	Gln	Gly	Gln		Leu	Ser	Ala	Tyr		Ala	Pro	Ser	
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Pro	120	Ala	HIS	ser	GIY		His	Arg	Tyr	GIN		Pne	vaı	ıyr	Leu	
cad		aas	220	ata	250	125	ctc	ctt	ccc	220	130	220	222	act	caa	530
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	tct	taa	aaa	atq		aga	ttt	ctg	aac		ttc	cac	cta	qqc		578
								Leu								
•		•	•	155	-	•			160	-				165		
cct	gaa	gca	agc	acc	cag	ttc	atg	acc	cag	aac	tac	cag	gac	tca	cca	626
Pro	Glu	Ala	Ser	Thr	Gln	Phe	Met	Thr	Gln	Asn	Tyr	Gln	Asp	Ser	Pro	;
			170					175					180			
								gcc								674
Thr	Leu		Ala	Pro	Arg	Glu		Ala	Ser	Glu	Pro	_	His	Lys	Asn	
		185	- 4				190					195			_	700
							taga	atago	cg (	gctti	rgcca	at C	eggg	catg		725
GIN	200	GIU	тте	ата	Ala	-										
aac		cta 4	~~~~	7020	-cr -24	205	rtaa	n +=+	-00-	2000	cct	-t.c.	ata 4	ים תים:	acccct	785
		-			_			a aaa				99	uca (	-uya		826
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aaacggcgtc acc atg atc gca cgg cgg aac cca gta ccc tta cgg ttt
                                                                       109
               Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe
                    -40
                                        -35
ctg ccg gat gag gcc cgg agc ctg ccc ccg ccc aag ctg acc gac ccg
                                                                       157
Leu Pro Asp Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro
                -25
                                     -20
egg etc etc tac atc gge tte ttg gge tac tge tec gge etg att gat
                                                                       205
Arg Leu Leu Tyr Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp
            -10
                                 -5
aac ctg atc cgg cgg agg ccg atc gcg acg gct ggt ttg cat cgc cag
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Asn Leu Ile Arg Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln
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ctt cta tat att acg gcc ttt ttt ttg ctg gat att atc ttg
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Leu Leu Tyr Ile Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu
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                                         30
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                                                                      355
tacatccaga ggattttcct gaagaagata agaaaacata tggtgaaatt tttgaaaaat
                                                                      415
tccatccaat acgttgaagt cttcaaaatg cttgctccag tttcactgat acctgctgtt
                                                                      475
cctgaatttg atggaacatg tttcttatga cagttgaagc ttatgctaat ctgtatgttg
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gactttgtgc ctatggttgg ggacagagtg aggtcgttgc cttgacgacg acagcatgcg
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gecegtggte etectaagtg tgagettgeg geggaeegag geceaeetge etecetgeet
                                                                      240
gettegecca ggaetegtga etgegteege agaagaaate acaacagege tggaattget
                                                                      300
agtttgctag gcagcatctt ttggacctgc gaaccatatg catttcacct caaatctgtt
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tccaagttga aaacctttgg gtctttctat gcgaacggat tgaagaaacg caaaaagttt
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aga	att	gtg	gcc	ata	aag	aag	ttc	tta	gaa	agt	gac	gat	gac	aaa	atg	568
								Leu								
_		30					35					40				
gtt	aaa	aag	att	gca	atg	cga	gaa	gtc	aag	tta	cta	aag	caa	ctt	agg	616
Val	Lys	Lys	Ile	Ala	Met	Arg	Glu	Val	Lys	Leu	Leu	Lys	Gln	Leu	Arg	
	45					50					55			•		
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His	Glu	Asn	Leu	Val	Asn	Leu	Leu	Glu	Val	Cys	Lys	Lys	Lys			
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										Met	t Ly	s Ar	g Let	ي Le	ı Pro	
											-1!					
								ctg								103
Ala	Thr	Ser	Leu	Ala	Gly	Pro	Val	Leu	Ser	Thr	Leu	Ile	Ala	Pro	Thr	
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ccc	atg	ttg	ttt	tgt	gaa	gat	aaa	agc	tgg	gat	ctt	ttt	ctt	ttt	ttt	151
Pro	Met	Leu	Phe	Cys	Glu	Asp	Lys	Ser	Trp	Asp	Leu	Phe	Leu	Phe	Phe	
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Lys	Ser	His	Lys	Thr	Trp	Gly	Ile	Ser	Thr	Asn	Leu	Ser	Ser	Cys	Pro	
		25					30					35				
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Phe	Gly	Asn	Leu	Phe	Leu	Cys	Val	Gln	Phe	Val	Arg	Glu	Lys	Gln	Ser	
	40					45					50					
ttt	tgt	atg	aat	aca	gaa	tgt	gat	tta	cgc	aag	aat	tga	caaa	aaa		293
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5,5					60					65						
aaa	aaaa	a														301
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                                                                      120
atg gcg gag ccg tcg gcg gcc act cag tcc cat tcc atc tcc tcg tcg
                                                                      168
Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser Ser
    -55
                        -50
                                             -45
tec tte gga gee gag eeg tee geg eec gge gge ggg age eea gga
                                                                      216
Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Gly Ser Pro Gly
                    -35
                                         -30
ged tgd ded ged etg ggg adg aag agd tgd agd ted ted tgt geg gat
                                                                      264
Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp
                -20
                                     -15
tee ttt gtt tet tee tet tee tet cag eet gta tet eta ttt teg acc
                                                                      312
Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr
tca caa gag gga ttg agc tct ctt tgc tct gat gag cca tct tca gaa
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Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu
                        15
                                             20
att atg act tct tcc ttt ctt tca tct tct gaa ata cat aac act ggc
                                                                      408
Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly
                    30
                                         35
ctt aca ata cta cat gga gaa aaa agc cat gtg tta ggg agc cag cct
                                                                      456
Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro
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att tta gcc aaa aaa aaa aaa
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Ile Leu Ala Lys Lys Lys
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 Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala
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gcc tct gag gct gcg tgc ctg atc gtg tct gta gat gaa acc atc aag
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Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys
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aac ccc cgc tcg act gtg gat gct ccc aca gca gca ggc cgg ggc cgt

PCT/IB98/02122 ·

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Gly Arg Gly Arg Pro His  50  ctggctgctg ggtgcactta ccctccttgg cttggttact tcattttaca aggaaggggt 2  agtaattggc ccactctctt cttactggag gctatttaaa taaaatgtaa gacttcaaaa 3	93 <sup>°</sup>
Gly Arg Gly Arg Pro His  50  ctggctgctg ggtgcactta ccctccttgg cttggttact tcattttaca aggaaggggt agtaattggc ccactctctt cttactggag gctatttaaa taaaatgtaa gacttcaaaa 3	93
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andadada	23
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Met Leu Thr Leu	
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tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys -10 -5 1 5	
tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys -10 -5 1 5 att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg	105 153
tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys -10 -5 1 5 att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met 10 15 20	153
tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc  Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys  -10  -5  att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg  Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met  10  15  20  tgc ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gag	
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tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc  Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys  -10  -5  att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg  Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met  10  15  20  tgc ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gag gag  Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Glu Glu  25  30  35  cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac	153
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tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc  Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys  -10  att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg  Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met  10  15  20  tgc ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gag gag  Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Glu Glu  25  cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac  Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu Asp Asp  40  45  acc att gca atc att gat gtg cct gtc ccc agt ttc tct gat agt gac  Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe Ser Asp Ser Asp  50  cct gca gca att att cat gac ttt gaa aag gga atg act gct tac ctg	153 201 249
tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc  Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys  -10  att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg  Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met  10  15  cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Gly Glu  25  cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac  Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu Asp Asp  40  acc att gca atc att gat gtg cct gtc ccc agt ttc tct gat agt gac  Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe Ser Asp Ser Asp  50  cct gca gca att att cat gac ttt gaa aag gga atg act gct tac ctg  Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met Thr Ala Tyr Leu	153 201 249
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tta ggc ctt tca ttc atc ttg gca gga ctt att gtt ggt gga gcc tgc  Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val Gly Gly Ala Cys  -10  att tac aag tac ttc atg ccc aag agc acc att tac cgt gga gag atg  Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr Arg Gly Glu Met  10  15  cct ttt ttt gat tct gag gat cct gca aat tcc ctt cgt gga gag gag  Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu Arg Gly Glu Glu  25  cct aac ttc ctg cct gtg act gag gag gct gac att cgt gag gat gac  Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile Arg Glu Asp Asp  40  acc att gca atc att gat gtg cct gtc ccc agt ttc tct gat agt gac  Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe Ser Asp Ser Asp  50  cct gca gca att att cat gac ttt gaa aag gga atg act gct tac ctg  Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met Thr Ala Tyr Leu  75  gac ttg ttg ctg ggg atc tgc tat ctg atg ccc ctc aat act tct att  Asp Leu Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu Asn Thr Ser Ile	1153 2201 249  2297
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Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg Arg Asp Leu Leu 155 160 165	585
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Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 45	
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Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu 50 55	<del>-</del>
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Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg	301
75	
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1,7, 1,75

 $\dot{z}_{i}$ 

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Glu Pro Pro Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg 20 25 30	
cag gca gaa agg ctg ttt gaa aat caa ctt gtt gga ccg gag tcc ata Gln Ala Glu Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile	313
35 40 45	26-
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	cct															457
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	Ile															303
017			100	0-1			1	105					110		-1 -	
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Lys	Gly	Leu	Phe	Glu	Val	Asn	Pro	Trp	Lys	Arg	Glu	Val	Lys	Leu	Leu	
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	ctt															649
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	Asp	_		-	_											
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	Glu															237
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Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
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Caa gtg tgg aac acc acc atg aaa ggg ctc aag tgc cgt ggc ttc acc Gln Val Trp Asn Thr Thr Met Lys Gly Leu Lys Cys Arg Gly Phe Thr 65 70	400
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cccctatctc cagacctcat tcgcaatgaa gtagaatgtc tgaaagcaga tttcaaccac agaatcaagg aggttctct caactccctc ttcagtgcct actatgttgc atttctcccc ctgtgttttg tgaagagtac ccagtactat gac atg cgc tgg tca tgt gag cac Met Arg Trp Ser Cys Glu His -115 -110  ctc gtt atg gtg tgg atc aat gct ttt gtc atg ctc acc acg caa ctg Leu Val Met Val Trp Ile Asn Ala Phe Val Met Leu Thr Thr Gln Leu -105 -100 -95  ttg cca tcc aaa tac tgt gat ttg cta cat aaa tca gct gct cac ctg Leu Pro Ser Lys Tyr Cys Asp Leu Leu His Lys Ser Ala Ala His Leu -90 -85 -80  ggc aag tgg cag aag ttg gaa cat ggg tcc tac agc aat gct cca cag Gly Lys Trp Gln Lys Leu Glu His Gly Ser Tyr Ser Asn Ala Pro Gln -75 -70 -65  cac att tgg tca gaa aat aca ata tgg cct caa ggg gtg ctg gtg cgg His Ile Trp Ser Glu Asn Thr Ile Trp Pro Gln Gly Val Leu Val Arg -60 -55 -50 -45	120 174 222 270
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70 60 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 85 80 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 100 95 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 120 115 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 130 135 125 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 145 150 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 160 165 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 180

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Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr 60

Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn 75

Pro Ser Thr Phe Arg Gly Gln Val 95

-119-

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WO 99/31236 <211> 43. <212> PRT <213> Homo sapiens <400> 153 Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val 10 · Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys 25 Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp 40 35 <210> 154 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1 <400> 154 Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro -35 -30 -25 Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe -15 Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala 1 5 Gln Glu <210> 155 <211> 153 <212> PRT <213> Homo sapiens <400> 155

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Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
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Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val
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Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
                            40
Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
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                                        -75
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                                    -60
Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
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Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
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                            -30
                                                -25
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Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-10

-15

Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr 20 . 15 Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu 35 Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala 55 50 Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 70 65 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln 85 80 Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 100 95 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Ala Thr Ser Gln 115 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 130 135 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 150 145 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn 160

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155 150 145 Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu 170 . 175 165 Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro 190 185 180 Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln 195 200 . 205 Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys 215 220 Ser Thr Phe Ile 225

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<400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -55 -50 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -30 -35 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -20 -15 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys 1 -5 Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 10 15 Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 30 Ile Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 65 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 80 75 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 115 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Glu Asp 125 130 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 145 140 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 155 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 175 170 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro 190 195 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 220 225 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met 250

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -80..-1

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WO 99/31236
                                    -125-
                           -25
                                              -20
Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
 -15
                  -10
Ser Thr Gln Pro Val Pro Leu Cys Ser
               5
<210> 165
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 165
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
                   -10
                            ~5
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
                               10
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
       20
                        25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                     40
                                         45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
                   55
                                     60
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
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<222> -36..-1 <400> 166 Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn -30 -25 Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly -15 -10 Phe Gly Leu Gly Lys Val Ser Tyr Ile Gly Val Cys Gln Ser Lys Phe 1 5 His Phe Phe Glu Asp Gln Leu Arg Gly Ala Gly Phe Gly Pro Gln His 15 20 25 Asn Arg His Cys Leu Leu Thr Cys Glu Glu Cys Lys Ile Lys His Gly 35 40 Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser 50

<210> 167
<211> 351
<212> PRT

<221> SIGNAL

<213> Homo sapiens

<220>
<221> SIGNAL
<222> -16..-1

<400> 167 Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10 Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10 Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile 20 25 Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40 Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 55 Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 75 70 Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 90 85 Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 105 100 Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 115 120 125 Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135 140 Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155 Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 165 170 Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 185 190 180 Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu . 200 205 195 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 230 235 Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp 250 245 Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 270 265 260 Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 275 280 Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys . 295 300 His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys 310 \ 315 His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

330

<210> 168

<211> 138

<212> PRT

<213> Homo sapiens

325

<220>

<221> SIGNAL

<222> -47..-1

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en en la companya de la companya del companya de la companya del companya de la companya del la companya de la companya del la companya de la

<400> 168 Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu -40 -35 Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser -30 -25 -20 Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile - 5. -10 Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu . 10 Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile 25 Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu 40 Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe 55 60 Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu 70 75 Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala

WO 99/31236

<210> 169 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -73..-1 <400> 169 Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg -70 -65 Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val -50 -45 -55 Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr -35 -30 Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe -15 -20 Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile -5 1 Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile 10 15 Pro Leu Gly Thr Pro 25

and the control of the first of the control of the

Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -30 -35 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 15 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 120 115 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 125 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys 180

<210> 171 <211> 350 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

<400> 171 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 -50 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -30 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -5 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 10 1 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 40 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 45 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 . Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala

PCT/IB98/02122 -

Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 100 105 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 120 115 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 165 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 180 175 185 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 195 200 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 210 215 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 240 245 250 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 255 260 265 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

<210> 172 <211> 390 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -68..-1

<400> 172

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115

Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 125 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 160 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 180 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 215 220 210 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 230 235 225 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 245 250 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 265 260 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 290 295 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 Glu Gly Thr Ser Ala Ser 320

<210> 173 <211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -55 -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -10 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 25 20 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 35 40 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 55 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 75 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85

Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

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95

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105

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<210> 174
<211> 285
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -232..-1
<400> 174
Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile
           -225 -220
     -230
Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu
          -210
                                   -205
Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg
       -195 -190 -185
Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu
             -180 -175
Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg
         -165 -160 -155
Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val
                              -140
      -150
                       -145
Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile
        -130
                                     -125
Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys
-120
                -115
                                 -110
Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe
             -100
                              -95
Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp
         -85
                          -80
                                   -75
Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn
      -70
                       -65
                                        -60
Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn
  -55
                   -50
                                     -45
Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile
              -35
                               -30
Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala
             -20
                             -15
Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val
                         1 .
Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile
           15
                                    20
Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu
               30
                     35
Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys
             45
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<210> 175

<211> 153

<212> PRT

<213> Homo sapiens

<400> 175

Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 1 5 10 15
Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu

Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu 55 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 70 75 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 85 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 110 105 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 125 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly 150

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL

<222> -24..-1

Pro Pro Arg 75 and for the extreme that the company the end of the extrement of the extrementary of the extrement of the ex

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<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
                            -30
                                                -25
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
   -20
                        -15
                                            -10
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
-5
                    1
                                    5
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
            15
                                20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
                            35
                                                40
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
    45
                        50
                                            55
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Leu Phe Leu Leu Phe Phe Phe
            -20
                                -15
                                                    -10
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
        -5
                            1
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
                   15
                                        20
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
                30
                                    35
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
            45
                                50
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
                            65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                        80
Gln Lys Leu Ala Lys Lys Met Phe Phe
90
                    95
<210> 180
<211> 59
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<211> 59 <212> PRT <213> Homo sapiens

<400> 180

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

al da latar en en en la secretario de distante di a despression des dilas della tradación en entre deservición della contra de del en en especial della contra della del

<211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 60 55

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

Tyr Arg Ile Cys Asp Leu 70

<210> 181

<400> 182 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -45 -55 -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -25 -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu 15 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 65 Ser Leu Gln Asp Ala Leu Leu Leu Leu Met Gly Leu Gly Pro Leu and the contract of the contra

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To some series of the series o
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<211> 80
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -35..-1
<400> 183
Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
          -30
                                    -25
Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala
                                -10
Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
           1
               5
                                     10
Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
   15
                  20
Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
                                   40
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<210> 184
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 184
Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
  -20 · -15
                                        -10
Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
-5
                 1
Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
                             20
Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                                           40
Cys Gly Asn Ile Cys Met Ser Ile Leu
   45
```

and a substitution of the contract of the cont

Ile Ser Lys Arg Glu Gln Leu Glu Gln Gln Val Pro Glu Asn Tyr Phe 25 Tyr Val Pro Asp Leu Gly Gln Val Pro Glu Ile Asp Val Pro Ser Tyr 40 Leu Pro Asp Leu Pro Gly Ile Ala Asn Asp Leu Met Tyr Ile Ala Asp 55 Leu Gly Pro Gly Ile Ala Pro Ser Ala Pro Gly Thr Ile Pro Glu Leu 75 70 Pro Thr Phe His Thr Glu Val Ala Glu Pro Leu Lys Thr Tyr Lys Met 90 Gly Tyr

<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 186 Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu -15 -10 Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val 1 Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val 15 Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp Thr Pro 35 Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe Gln Lys 50 Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys Gln Thr 65 His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp His Arg 85

<210> 187 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1 <400> 187 Met Cys Cys Tyr Cys Arg Ile Phe Cys Leu Arg Cys Thr Tyr Phe Pro -40 Val His Cys Gly Met Cys Asn Leu Arg Tyr Phe Glu Phe Ser Thr Phe -25

-20 Leu Leu Ser Leu Ser Leu Ile Thr Tyr Cys Phe Trp Asp Pro Pro His -5 Arg Gly Ser His Ser Leu Ser Leu Glu His Thr Pro Leu Asp Phe Leu 10 Glu Trp Gly Leu Leu Arg

-35

<210> 189 <211> 207 <212> PRT

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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Leu Ser Asn Leu Asn Gln Ile Gly Ser
     -10
                              -5
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                   10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                  25
                                     30 .
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
                                  45
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
                              60
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
                           75
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<213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 189 Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile -5 Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 10 15 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys 25 30 Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met 45 Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu 60 65 Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile 75 80 Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu 90 95 Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys 110 115 Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro 125 130 Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu 135 140 145 Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

<210> 190

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155 . 160

165

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<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                                   10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
           20
                               25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                           40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                       55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                                   90
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
                           105
                                                  110
          100
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
      115
                           120
                                               125
Thr Met Glu Leu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                       135
                                           140
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
                   150
                                       155
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
                                   170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
           180
                                185
Asp Thr Val Lys Ile Gln Lys Lys
       195
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<210> 191

<211> 379

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 191

Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His
-35
-30
-25

Gly Ala Gln Lys Ala Ala Leu Val Leu Leu Ser Ala Cys Leu Val Thr
-20 -15 -10

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
15 20 25

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser 30 35 40

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
45 50 55

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

```
65
                                       70
Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
               80
                                   85
Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
                               100
Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
                           115
Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
                      130
                                        135
Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
                  145
                                      150
Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
              160
                                  165
Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
                              180
          175
Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
       190
                          195
                                             200
Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                       210
                                          215
Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
220
                   225
                                       230
Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
              240
                                   245
Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
           255
                               260
Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
                           275
                                              280
Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
                       290
                                          295
Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
                  305
                                      310
Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met
              320
                                  325
Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser
```

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

<400> 192 Met Pro Ser Glu Gly Arg Cys Trp Glu Thr Leu Lys Ala Leu Arg Ser 10 Ser Asp Lys Gly Arg Leu Cys Tyr Tyr Arg Asp Trp Leu Leu Arg Arg 20 25 Glu Asp Val Leu Glu Glu Cys Met Ser Leu Pro Lys Leu Ser Ser Tyr 40 45 Ser Gly Trp Val Val Glu His Val Leu Pro His Met Gln Glu Asn Gln 55 60 Pro Leu Ser Glu Thr Ser Pro Ser Ser Thr Ser Ala Ser Ala Leu Asp 70 75 Gln Pro Ser Phe Val Pro Lys Ser Pro Asp Ala Ser Ser Ala Phe Ser 90 Pro Ala Ser Pro Ala Thr Pro Asn Gly Thr Lys Gly Lys Lys Lys

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<211> 43 <212> PRT <213> Homo sapiens

Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys 35

<210> 194 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

<210> 195 <211> 244 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

35

<400> 195 Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala -10 Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile 25 20 Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys 40 35 Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp 55 Val Thr Glu Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly 70 75 Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala 90 85 Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe 105 Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr and a few consistency of the control of the control

```
115
                                 120
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
          130
                             135
                                               140
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
       145
                         150
                                            155
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
                      165
                                        170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
                 180
                                    185
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Ala Glu Val
            195
                       200
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
          210
                             215
Arg Thr Ala Trp
       225
```

<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 -20 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 1 5 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 25 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 35 4.0 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 140 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 145 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 180 185 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 220 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly

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WO 99/31236

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys Lys 20 25 30

<210> 198
<211> 112
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1

<400> 198 Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -40 -35 -45 Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -30 -25 Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -10 -5 Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val 5 . 10 15 Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 25 20 Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40 45 Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His

<210> 199
<211> 54
<212> PRT
<213> Homo sapiens
<400> 199
Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr
1 5 10 15

 Pro
 Arg
 Trp
 His
 Arg
 Leu
 Pro
 Pro
 Gln
 Ser
 Leu
 Gln
 His
 His
 Gln
 Tyr

 Cys
 Gln
 Arg
 Arg
 Trp
 Pro
 Asp
 Arg
 Arg
 Cys
 Leu
 Gln
 Ser
 His
 Thr
 Gln

 Ser
 Ser
 Gly
 His
 Leu
 Pro
 From the control of the c

<210> 200 <211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 200 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 . -10 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 1 Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Ile Thr Glu Glu Asp 50 ..55 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 70 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 80 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100 105 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 110 115 Gly Lys Val Lys Ser Phe Lys 125

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

<400> 201 Met Ser Met Ala Val Glu Thr Phe Gly Phe Phe Met Ala Thr Val Gly -10 -20 -15 Leu Leu Met Leu Gly Val Thr Leu Pro Asn Ser Tyr Trp Arg Val Ser -5 1 Thr Val His Gly Asn Val Ile Thr Thr Asn Thr Ile Phe Glu Asn Leu 15 20 Trp Phe Ser Cys Ala Thr Asp Ser Leu Gly Val Tyr Asn Cys Trp Glu 30 35 Phe Pro Ser Met Leu Ala Leu Ser Gly Tyr Ile Gln Ala Cys Arg Ala 50 45

Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly 60 Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg 80 Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly 95 Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 115 110 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 145 140 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 160 155 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 175 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg 190 Asn Ala Tyr Val 200

المائية والمرازي والمناه للمستقوم فالمائي المرازية والمعتقد بالمعالية المرازي والمرتبي المرازية والمستقد فالمشتوط سيعته

WO 99/31236

<210> 202

<211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1 <400> 202 Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly -40 -35 Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser -20 -25 Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe - 5 ~10

Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15 -10 -5 1
Pro Asp Leu Pro Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr
5 10 15

<210> 203 <211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1

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Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile Asp Arg Glu Asn
                        40
Phe Val Asp Ile Val Asp Ala Lys Leu Lys Ile Pro Val Ser Gly Ser
                                       60
Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg Gly Gly Pro Phe
                70
Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu Lys Asp Gly Gln
                               90
Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly Asp Glu Val Lys
Lys Glu
   115
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<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<400> 204 Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His Leu 20 25 Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro Glu 35 40 45 Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser 55 60 Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu 65 70 75 80 Glu Val Asp Asp Trp Glu Phe 85

<210> 205 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<400> 205 Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 -15 Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 -5 1 Leu Ser Leu Arg Ser Ala Met Ser 10

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206 Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg to settle in the contract of t

10 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 25 30 20 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro 45 40 35 Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 60 55 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 75 70 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 85 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 100 105 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 125 120 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr
85 90 95

Lys Gln Thr Ser Val

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -22..-1

 description of the contraction of the property of the contraction of t

```
35
          30
Glu Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                50
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Lys Lys Cys
                   65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
               80
                       85
Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
                   100
           95
Asp Glu Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
                                 120
         110 115
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
                              135
             130
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
                   145
                                    150
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
      160
                               165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
                            180
             175
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
                          195
                                           200
          190
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
                       210
                                       215
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                   225
                                    230
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
               240
                                245
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
            255
                             260
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
         270
                          275
                                           280
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
                       290
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                   305
                                    310
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
                                 325 330
                320
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                            340
     335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
                          355
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
                       370
     365
                                       375
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
   380 385 390
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
       400
                                405
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
             415
Gln Pro Cys Leu Tyr Lys Arg Arg
          430
```

<210> 209 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

<400> 209 Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp -10 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 5 10 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 25 20 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 35 40. Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 60 55 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln 70 Val Glu 80

<210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> 51GNAL <222> -29..-1

<210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1

```
50
          45
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                       65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                                     85
                    В0
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn
                                 100
                95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
                      115
             110
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile
                                   135
                  130
         125
Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu
                               150
                145
Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe
                              165
            160
Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val
                        180
        175
Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys
           190
                              195
Arg Lys Ser Arg Thr
          205
```

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly 1 Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 40 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 55 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 70 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 80 . Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 105 100 95 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 110 Asn Asp Phe Ser Gln Glu Ser Ser 130 125

<210> 213 <211> 179 <212> PRT <213> Home sapiens <221> SIGNAL <222> -54..-1 <400> 213 Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr -45 Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala -30 ~35 Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala -15 -10 Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys 1 Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro 20 Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu 35 Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu 50 55 Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu 70 65

Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser 75 80 85 90

Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp 95 100 105

Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met 110 115 120

Asn Leu Ile 125

<220>

<210> 214

<211> 269

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -92..-1

<400> 214

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu
-90 -85 -80

Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro
-75 -70 -65

Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp
-60 -55 -50 -50

Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr

-40 -35 -30
Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala

-25 -20 -15
Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val

-10 -5

Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val
5 10 15 20

Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe 25 30 35

Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys
40 45 50

His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr
55 60 65

Controller on the Section of the Control of the Con

Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn 75 Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala 90 Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln 110 105 Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu 125 His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp 140 145 Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr 160 150 155 Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro 170

<210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 215 Met Gln Thr Val Tyr Tyr

110

-20

Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala 1 5 Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 15 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile . 30 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 80 85 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 95 100 Ser Ala Pro Lys Ser Asn Val

-15

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -45 -50 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala -30 -35 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -15 -20 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro 5 1 Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 15 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn

50

Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr
60 65 70

<210> 218 <211> 376 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

45

<400> 218 Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Pro Pro -10 -15 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 20 25 15 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 55 50 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 70 65 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe 85 Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

```
100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
                        115
                                  120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                    130
                                        135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                  145
                                     150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
              160
                                  165
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
          175
                             180
                                                 185
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                         195
                                            200
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
                     210
                                        215
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
                  225
                                     230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
              240
                                 245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
           255
                             260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
                         275
                                   280
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                      290
                                         295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                  305
                                     310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
              320
                                 325 ..
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
          335
Arg Ser Tyr Leu Pro Gln Ile Ser
       350
```

<210> 219 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 219

<222> -30..-1

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arq Arq His Leu Leu Val -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro -10 - 5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 15 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 30 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe 90

Andropa - Santa and the control of the Mandelman to the transfer of the transfer of the control of the transfer of the control of the transfer of the control of the contro

His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro 105 110 Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser 120 125 115 Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly 135 140 Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser Ser His Ser 155 150 Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser 170 Arg Gln Leu 180

<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -60..-1

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90

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190

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-20 - 15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp

Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20

Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 35

Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 50 55

Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70

Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr

Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100

Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120

Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135

Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150

His Leu Leu Ala Asp Thr Met Leu 160

<210> 225

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<222> -22..-1

<400> 225

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -15

Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His

Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 20

Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 35

Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50

Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp

Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80

85 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile

100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His

115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys

130 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys

145 150 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser

160 165 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile
190 195 200

Ala Ala Cys
205

<211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 226 Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu -30 -35 Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr -15 -20 Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg -5 1 Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile 15 Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu 30

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<210> 226

<210> 228
<211> 82
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Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

<210> 229

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Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly
                  -35
                                     -30
Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp
               -20
                                -15
Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr
           -5
                             1
Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu
                     15
                                        20
Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly
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                                     35
Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro
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Ile Leu Ala Lys Lys Lys
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<210> 230

<220>
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<222> -14..-1

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185

<210> 232 <211> 108 <212> PRT <213> Homo sapiens

Gln Glu 195

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<210> 233 <211> 43

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<221> SIGNAL
<222> -18..-1
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Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
- 1 5 - 10

Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
- 25

<210> 234 <211> 36 <212> PRT <213> Homo sapiens

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Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 Trp Gln Arg Arg Asp Tyr Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 180 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 220 225 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 230 235 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 245 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala 285 Lys Lys Lys

<210> 236 <211> 106 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -32..-1

<400> 236

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<210> 237 <211> 42 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

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 <211> 117
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                                        -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
                1
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
        15
                           20
                                              25
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                       35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
                                    _ . . 55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
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                                    70
Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile
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                              85
Ile Asp Lys Thr Thr
        95
<210> 239
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Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
       -35
                            -30
                                               -25
Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
    -20
                        -15
                                           -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                   7
                                  5
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu
                                20
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 11e
 Ser
 Arg
 Tyr
 Ala
 Thr
 Ala
 Pro
 Thr
 Asp
 Ile
 Glu
 Ser
 Gly
 Thr
 Val

 Asp
 Cys
 Val
 Lys
 Leu
 Thr
 Phe
 Ser
 Pro
 Pro
 Pro
 Leu
 Leu
 Val
 Asp

 Val
 Thr
 Asp
 Gln
 Val
 Tyr
 Glu
 Tyr
 Lys
 Arg
 Glu
 Ile
 Ser
 Gln

 Val
 Thr
 Asp
 Gln
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 Tyr
 Lys
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 His
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 Gly
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 Arg
 Ile
 Leu
 Glu
 Lys
 Met
 Thr

 Asp
 Ile
 Asp
 Pro
 His
 Gln
 Asp
 Val
 Lys
 Arg
 Ile
 Lys
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100 105 95 His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly 115 120 110 Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val 125 130 135 Ile Gly 140 <210> 240 <211> 126 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1 <400> 240 Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val -20 Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser -10 1 - 5 Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile Phe Ile 10 15 Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala 30 Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr 45 50 Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly 65 60 Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro 80 75 Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys <210> 241 <211> 174 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -115..-1 <400> 241 Met Arg Trp Ser Cys Glu His Leu Val Met Val Trp Ile Asn Ala Phe -110 -105 Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu -95 -90 His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly -75 Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp -55 -60 Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met -45 -40 Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe

-30

-25

Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu

25

-10

Ile Glu Gly Gly Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg Ser 5

Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys Asn

20

15

-15

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Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Ile Val Leu Gly Arg
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Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn
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                   Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val
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                                       -15
ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                       98
Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
                -5
aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gct gcc
                                                                      146
Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                            15
cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                      193
His His Phe Ile His Pro Cys Leu Asp
aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
                                                                      253
agagggcage acttatacet ggtggtettt etgatggtea gttttattee ceteetgaat
                                                                      313
ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
                                                                      373
tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaag
                                                                      433
aggcaggcag tggagtetee etgtegacag taaagttgaa atggtgacgt ecactgetgg
ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
tecatgeaca tttagttgcc tgcctgtggc tggtaaggta atgtcatgat tcatcctctc
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ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
                                                                      733
tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt
                                                                     793
tttaacactc tacatttccc ttgtttttta actcatgcac atgtgctctt tgtacagttt
                                                                      853
taaaaagtgt aataaaatct gacatgtcaa araaaaaaaa mcy
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WO 99/31236

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<222> 17..85

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<221> polyA\_signal <222> 820..825

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                                                                       112
                                Met Ala Phe Thr Leu Xaa Ser Leu
                                                -10
ctg cag gca gcc ctg ctc tgc gtc aac gcc atc gca gtg ctg cac gag
                                                                       160
Leu Gln Ala Ala Leu Leu Cys Val Asn Ala Ile Ala Val Leu His Glu
gag cga ttc ctc aag aac att ggc tgg gga aca gac cag gga att ggt
                                                                       208
Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly Thr Asp Gln Gly Ile Gly
                15
                                     20
gga ttt gga gaa gag ccg gga att aaa tca sag sta atg avs ctt att
                                                                      256
Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser Xaa Xaa Met Xaa Leu Ile
            30
                                 35
cga tet gta aga ace gtg atg aga gtg cca ttg ata ata gta aac tca
                                                                      304
Arg Ser Val Arg Thr Val Met Arg Val Pro Leu Ile Ile Val Asn Ser
                            50
att gca att gtg tta ctt tta tta ttt gga tgaatwtcat tggagaaaat
                                                                      354
Ile Ala Ile Val Leu Leu Leu Phe Gly
                        65
ggakactcag aaraggacat gccaktaraa kttattactt tggtcattat tggaatattt
atatettage tggetgacet tgeaettgte aaaaatgtaa agetgaaaat aaaaceaggg
                                                                      474
tttctattta aaaaaaaaa a
                                                                      495
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tgaggagctg gagctggtgg ggactgggcc gca atg gac aag ctg aag aag gtg
                                      Met Asp Lys Leu Lys Lys Val
                                      -55
ctg agc ggg cag gac acg gag gac cgg agc ggc ctg tcc gag gtt gtt
                                                                      162
Leu Ser Gly Gln Asp Thr Glu Asp Arg Ser Gly Leu Ser Glu Val Val
            -45
                                 -40
gag gca tct tca tta agc tgg agt acc agg ata aaa ggc ttc att gcg
                                                                      210
Glu Ala Ser Ser Leu Ser Trp Ser Thr Arg Ile Lys Gly Phe Ile Ala
                            -25
                                                 -20
tgt ttt gct ata gga att ctc tgc tca ctg ctg ggt act gtt ctg ctg
                                                                      258
Cys Phe Ala Ile Gly Ile Leu Cys Ser Leu Leu Gly Thr Val Leu Leu
                         -10
                                             -5
tgg gtg ccc agg aag gga cta cac ctc ttc gca gtg ttt tat acc ttt
                                                                      306
Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe
                                    10
ggt aat atc gca tca att ggg agt acc atc ttc ctc atg gga cca gtg
                                                                      354
Gly Asn Ile Ala Ser Ile Gly Ser Thr Ile Phe Leu Met Gly Pro Val
                                25
aaa cag ctg aag cga atg ttt gag cct act cgt ttg att gca act atc
                                                                      402
Lys Gln Leu Lys Arg Met Phe Glu Pro Thr Arg Leu Ile Ala Thr Ile
        35
                            40
                                                 45
atg gtg ctg ttg tgt ttt gca ctt acc ctg tgt tct gcc ttt tgg tgg
                                                                      450
Met Val Leu Cys Phe Ala Leu Thr Leu Cys Ser Ala Phe Trp Trp
                        55
cat aac aag gga ctt gca ctt atc ttc tgc att ttg cag tct ttg gca
                                                                      498
His Asn Lys Gly Leu Ala Leu Ile Phe Cys Ile Leu Gln Ser Leu Ala
                    70
                                        75
ttg acg tgg tac agc ctt tcc ttc ata cca ttt gca agg gat gct gtg
                                                                      546
Leu Thr Trp Tyr Ser Leu Ser Phe Ile Pro Phe Ala Arg Asp Ala Val
aaa aad tgt ttt gcc gtg tgt ctt gca taattcatgg ccagttttat
                                                                      593
Lys Xaa Cys Phe Ala Val Cys Leu Ala
            100
gaagetttgg aaggeactat ggacagaage tggtggacag ttttgtwact atettegaaa
                                                                      653
cctctgtctt acagacatgt gccttttatc ttgcagcaat gtgttgcttg tgattcgaac
                                                                      713
atttgagggt tacttttgga agcaacaata cattctcgaa cctgaatgtc agtagcacag
                                                                      773
gatgagaagt gggttctgta tcttgtggag tggaatcttc ctcatgtacc tgtttcctct
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ctggatgttg tcccactgaa ttcccatgaa tacaaaccta ttcagcaaca gcaaaaaaaa
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aaaa
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<222> 472..477
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<222> 507..518
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aggegeetge agg atg aaa get ete tgt ete ete ete eet gte etg
                                                                  109
              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
                          -15
ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                  157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
                      1
                                      5
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
                                  20
               15
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                  253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
                              35
                                                                  301
get act tgc ccc cga ggc ttc gcc gtc acc ggc tgc act tgt ggc tcc
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
                           50
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
                                                                  349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                       65
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
                                                                  397
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
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518
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<210> 249

<211> 996

<212> DNA

<213> Homo sapiens

<220>

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<222> 111..191

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<222> 111..155

<223> Von Heijne matrix
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 seq FLXLMTLTTHVHS/SA

<221> polyA\_signal

<222> 965..970

<221> polyA site

<222> 986..996

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ttc ctg wgt cta atg acc ctg aca acc cat gtt cac tca agt gcc aag 164

Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser Ala Lys -10 -5 1

cca aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat 211

Pro Asn Glu Gln Pro Trp Leu Leu Asn 5

ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt

ggctgcgatc accagctggg aagcaccgt			
	c aaggaarata	actgtggggt ctgcaacrga	331
natgggtcca cctgccggct ggtccgagg			391
torgatgata otgtggttgo aattoocta	t ggaagtakac	atattcgcct tgtcttaaaa	451
ggtcctgatc acttatatct ggaarccaw			511
ctcasctcca caggaacttt ccttgtgga			571
gacwdagaga tactgagaat ggctggacc			631
aactcgggct ccgctgacag tacagtcca			691
tggagggara cggatttctt tccttgctc			751
tcggctgagt gctacgatct gaggagcaa			811
tacccagaga acatcaaacc caaacccaa			871
gccaggtcag tcaaatttgc tagttcatt			931
ttatttaaat taaaatgaaa cgttttaat	t aaaaataaaa	tgaaattaaa catcaaaaa	991 996
aaaaa			330
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sed priinchiphikalõi			
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<222> 850860 <400> 250	a cccccagctc	cgac atg tcg ccc tct Met Ser Pro Ser -20	56
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の一般の一般の一般の一般の一般の一般の一般の一般の一般の一般の一般の一般の一般を表現して、一般の一般の一般の一般の一般の一般を表現しています。

gtc cat dac aga ccb cba kda ccc tca akc cat ctg gtt ttc atg agg Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu Val Phe Met Arg 100 105 110	440
atg acc cct tct tct atg atg aac aca ccc tcc gga aac sgg ggc tgt Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly Asn Xaa Gly Cys 115 120 125	488
tgg tcg cag ctg tgc tgt tca tca cag gca tca tca tcc tca cca gtg Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser Ser Fro Val 130 135 140	536
gca agt gca ggc agc tgt ccc ggt tat gcc gga atc att gca ggt gag Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile Ile Ala Gly Glu 145 150 155	584
tcc atc aga aac agg agc tgacaacctg ctgggcaccc gaagaccaag Ser Ile Arg Asn Arg Ser 160 165	632
ccccctgcca gctcaccgtg cccagcctcc tgcatcccct cgaagagcct ggccagagag ggaagacaca gatgatgaag ctggagccag ggctgccggt ccgagtctcc tacctcccc	692 752
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Cga cct gta ctc cag aat ctg ttg cag agc cca ggc ttg aca tgg agc Arg Pro Val Leu Gln Asn Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser 1 5 10 15	149
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aca gca aat cag gaa cta aac agg atg agg tet etg tet tet gge tee Thr Ala Asn Gln Glu Leu Asn Arg Met Arg Ser Leu Ser Ser Gly Ser	341
65 70 75 80	200
gtg cca gtg ggg cat ctg gag ggt ggc acg gtc aag ctt cag aag gac Val Pro Val Gly His Leu Glu Gly Gly Thr Val Lys Leu Gln Lys Asp 85 90 95	389
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Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr 100 105 110	
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Pro Ala Ser Val Leu Ala Asp Ala Cys Pro Gly Phe His Asp Val Xaa 115 120 125	
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Val Gln Xaa Ala Leu Phe Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys 130 135 140	
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Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu Thr Val Ala -35 -30 -25	261
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Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala Pro Phe Pro	
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Tyr Arg Tyr	
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Glu Lys Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His	
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- Dar rep ron rar ren ded ded ded aer aac act ded cou cuc aec cau	201

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gct Ala	ccg Pro	gag Glu	ctg Leu	gac Asp 180	gag Glu	gcc Ala	gaa Glu	ttg Leu	gac Asp 185	tac Tyr	ctc Leu	atg Met	gat Asp	gtg Val 190	ctg Leu	793
gtg Val	ggc Gly	aca Thr	cag Gln 195	gca Ala	ctg Leu	gag Glu	cga Arg	ccg Pro 200	ccg Pro	ggg Gly	cca Pro	GJA 888	cgc Arg 205			835
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Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr	
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Val Tyr Ala Leu Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile	
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Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val	
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Ala	Val	Thr	Ile		Cys	Thr	Phe	Ser		Thr	Gly	Cys	Pro		Glu	
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	cca			_			_			_		_				242
Gln	Pro	Thr	_	Leu	Trp	Phe	Arg	_	Gly	Ala	His	Gln		Glu	Asn	
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_	tgc	_	_		_		_		_	_	_			-		290
Leu	Сув		Asp	GIA	Cys	гàг		GIU	Ala	хаа	ьуs		Thr	vaı	Arg	
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	gcc Ala															330
	65	пеп	гур	GIU	ASII	70	vaı	Set	Deu	TIIL	75	ASII	AIG	vaı	1111	
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	Asn															500
80					85	-,-		-,-	01,	90					95	
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	Glu															
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	Glu															
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ctt	gta	tca	ctg	ctc	tct	gtc	tat	gtg	acc	ggt	gtg	tgc	gtg	gcc	ttc	530
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-	Glu	Asp	Ser	Gin	_	Lys	Lys	Ser	Ala	_	Arg	He	Phe	GIn		•
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	Glu			5-		,				- 5	,					
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uris Haly

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ctg ttt gca caa gct gag aag ttg tat ctt aag cta cag aca gac atc       403         Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu Lys Leu Gln Thr Asp Ile       5         tct gaa ctt gaa aac cga gaa tta tta gaa caa ktt gca gaa ttt gaa       451         Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu Gln Xaa Ala Glu Phe Glu       20       25         aaa gca rav att aca tct tca aac aaa aag ccc atc tta dat gtc aca       499         Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys Pro Ile Leu Xaa Val Thr       30       35       40         aas cca aaa ctt gct cca ctt aat gaa ggt gga aca gca aaa ctc cta       547         Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu       55         aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg       595         Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu       595         tcc tgt cat tgc cta ggg tgg aga aac aac aaa agt gga agg ttt gtt tca       60       65         tcc tgt cat tgc cta ggg tgg aga aac aac aaa agt gga agg ttt gtt tca       643         Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser       643
ctg ttt gca caa gct gag aag tgg tat ctt aag tta can can can gct gag aag tgg tat ctt aag tta can can can can can can can can can ca
tct gaa ctt gaa aac cga gaa tta tta gaa caa ktt gca gaa ttt gaa 451  Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu Gln Xaa Ala Glu Phe Glu  10
tct gaa ctt gaa aac cga gaa tta tta gaa caa ktt gca gaa ttt gaa       451         Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu Gln Xaa Ala Glu Phe Glu 10       15       20       25         aaa gca rav att aca tct tca aac aaa aag ccc atc tta dat gtc aca Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys Pro Ile Leu Xaa Val Thr 30       40       499         aas cca aaa ctt gct cca ctt aat gaa ggt gga aca gca aaa ctc cta Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu Asn Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu Asn Gly Lys Ser Leu Ile Leu Asn Gly Lys Ser Leu Ile Leu For Ser Leu Ile Leu For Ser Leu Ile Leu For Ser Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser       643
Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu Gln Xaa Ala Glu Phe Glu       10       15       20       25         aaa gca rav att aca tct tca aac aaa aag ccc atc tta dat gtc aca       499         Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys Pro Ile Leu Xaa Val Thr       30       35       40         aas cca aaa ctt gct cca ctt aat gaa ggt gga aca gca aaa ctc cta       547         Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu       55         aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg       595         Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu       60       65       70         tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca       643         Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser       643
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Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys Pro Ile Leu Xaa Val Inf 30 35 40  aas cca aaa ctt gct cca ctt aat gaa ggt gga aca gca aaa ctc cta Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu 45 50 55  aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu 60 65 70  tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser
aas cca aaa ctt gct cca ctt aat gaa ggt gga aca gca aaa ctc cta  Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu  45  aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg  Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu  60  65  70  tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca  Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser
Asa Pro Lys Leu Ala Pro Leu Asn Glu Gly Gly Thr Ala Lys Leu Leu  45  aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg  Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu  60  65  70  tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca  Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser
45  aac aag gta ata tgt att att ttg aga aac gga aag tct ctc att ctg  Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Leu  60  65  70  tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca  Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser
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Asn Lys Val Ile Cys Ile Ile Leu Arg Asn Gly Lys Ser Leu Ile Beu  60 65 70 tcc tgt cat tgc cta ggg tgg aga aac aaa agt gga agg ttt gtt tca Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser
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Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe val Ser
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Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln
90 95 ccatgggcca gaagagggca tacttaacct tctagagagc ctgaagtagc tcctgatcac 753
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Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro
                                         -50
                    -55
att cag gca ctt atg gcc att tca gcc act ttc aag atg tta gaa agt
                                                                       148
Ile Gln Ala Leu Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser
                -40
                                                                       196
tca age cag aag tit ett cag ggt tig gie tat ete att ggg aac etg
Ser Ser Gln Lys Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu
                                                     -15
                                 -20
            -25
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Met Gly Leu Ala Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu
                             -5
cct aca cat gca tcg gat tgg tta gcc ttc att gag ccc cct gag aga
                                                                       292
Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg
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Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala
                                     30
cct ggt ccc tat gta ttt ggg tct tat tta cat cct tct tta agc cca
                                                                       388
Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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                                 45
gtg gct cct cag cat act ctt aaa cta atc act tat gtt aaa aaa aac
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Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
                             60
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 caa aaa act ctt ttc tcc atg gtg ggg tgacaggtcc taaaaggaca
 Gln Lys Thr Leu Phe Ser Met Val Gly
 atgtgcatat tacgacaaac acaaaaaaac tataccataa cccagggctg aaaataatgt
                                                                       603
 aaaaaacttt atttttgttt ccagtacaga gcaaaacaac aacaaaaaaa cataactatg
 taaacaaaaa aataactgct gctaaatcaa aaactgttgc agcatctcct ttcaataaat
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caggagetee gggaggeagg geeggeeeea egteetetge geaceaceet gagttggate
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                                                                      240
egetgeeete etgeetgeag ee atg aeg eee etg ete aee etg ate etg gtg
                                                                      292
                         Met Thr Pro Leu Leu Thr Leu Ile Leu Val
                         -20
gtc ctc atg ggc tta cct ctg gcc cag gcc ttg gac tgc cac gtg tgt
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Val Leu Met Gly Leu Pro Leu Ala Gln Ala Leu Asp Cys His Val Cys
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gcc tac aac gga gac aac tgc ttc aac ccc atg cgc tgc ccg gct atg
                                                                      388
Ala Tyr Asn Gly Asp Asn Cys Phe Asn Pro Met Arg Cys Pro Ala Met
            10
                                15
gtt gcc tac tgc atg acc acg cgc acc tac tac acc ccc acc agg atg
                                                                      436
Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
                            30
aag gtc agt aag tcc tgc gtg ccc cgc tgc ttc gar nac tgt gta
                                                                      481
Lys Val Ser Lys Ser Cys Val Pro Arg Cys Phe Glu Xaa Cys Val
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caccggcctt gccaccccgg ccaccctggc cctggcccc atcctcctgg ccaccctctg
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gggtctcctc taaagccccc gaggcagacc cactcaagaa caaagctctc gagacacact
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gctayaccct ckcacccakc tcaccctgcc tcaccctcca cactccctgc gacctcctca
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gccatgccca gggtcaggac tgtgggcaag aagacacccg acctccccca accaccacac
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gacctcactt cgaggccttg acctttcgat gctgtgtggg atcccaaaag tgtccggctt
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Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly Leu Val Leu Ala Pro	
-15 -10 -5 1	152
cet tte tee tet eeg gge aet gae eee aee ttt eeg tgt att tae tgt	152
Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe Pro Cys Ile Tyr Cys  10 15	•
agg cta tta aat atg atc atg acc cgc ctt gca ttt tca ttc atc acc	200
Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala Phe Ser Phe Ile Thr	
20 25 30	
tgt tta tgc cca aat tta aag gaa gtt tgt ctc att ttg cca gaa aaa	248
Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu Ile Leu Pro Glu Lys	
35 40 45	
aat tgt aat agt cga cac gct gga ttt gta ggg cca sca aaa ttg cgg	296
Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly Pro Xaa Lys Leu Arg	
50 55 60 65	
cag tgaaactwkk ttcwcttcta aagcccttca tttcccacaa ggttaagctc	349
Gln	409
tegaaacccc atttgatect tggttectat ttegatecte etttggaate tgaaaategg	469
tetecatgtt gtatgcaaat taaaakttge ettgtttgtt actettecaa cacagggtat	529
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His

tgg cct cca ttc tcc sct ttc ctc tgt aca gtt tgc tct ggt tcc tca Trp Pro Pro Phe Ser Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser 10 15 20	326
gag cag att tcc gag tat act gct tca gcc acg ccc cca ctg tgc cgt Glu Gln Ile Ser Glu Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg 25 30 35	374
tcc ctg aac caa gag cca ttc gty tca aga gcc att cgt cca aag tac Ser Leu Asn Gln Glu Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr 40 45 50	422
tot atc acc tagecattgt akccatacca ageogggett cetaetteec Ser Ile Thr 55	471
totgotoccc ttggtttcct cctgtraart aaatctcact gacccttgat gcasctccaa	531
gcatatata tatatatata ataaaaccat abtctaaaaa attcaaacca ggawaaataa asccaraaat ttgtatggga aaaatctgca caaatttatt tggccagcat ggttatcatg	591 651
gctctattga atttatcctt gaccgtcttt aaagccaaag caaacgggat aaagtgatca	711
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scatctctact aaaattacaa aaaattrgct gggcgaggtg gcgggcacct gtggtcccag	951
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gcaaagccaa coctcaccgc tggtcggtgg gccatacc atg gga aag gga cat cag	240 296
Met Gly Lys Gly His Gln -25	
cgg ccc tgg tgg aag gtg ctg ccc ctc agc tgc ttc ctc gtg gcg ctg	344
Arg Pro Trp Trp Lys Val Leu Pro Leu Ser Cys Phe Leu Val Ala Leu -20 -15 -10	
atc atc tgg tgc tac ctg agg gag gag agc gag gcg gac cag tgg ttg	392
Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser Glu Ala Asp Gln Trp Leu	
-5 1 5 10	

440

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cct gag act cca gct gcc tac aga gcg aga act tgacggggtg cccgctgggg Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg Thr	493
ctggcaggaa gggagccgac asccgcctt cggatttgat ktcacgtttg cccgtgactg tcctggctat gcktgcgtcc tcagcactra argacttggc tggtggatgg ggcacttggc tatgctgat cgcgtgaagg cggavcaaaa tctcagcaaa tcggaaactg ctcctcscct ggctcttgat ktccaaggat tccatcggca aaacttctca ratccttggg gaaggtttca gttgcactgt atgctgttgg atttgccaag tctttgata acataatcat gtttccaaag cacttctggt gacacttgtc atccagtgtt agtttgcagg taatttgctt tctgagatag aatatctggc agaagtgtga aactgtattg catgctgcgg cctgtgcaag gaacacttcc acatgtgagt tttacacaac aacaaatgaa aataaatttt aattttataa tatgggaaaa aaaaaaaa	553 613 673 733 793 853 913 973 981
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aat aaa ttt gga gca gaa gag ara agc ctt att gga ctt tct ggc att Asn Lys Phe Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile 5	146
ttc atc ggc att gga gaa att tta ggt gga agc ctc ttc ggc ctg ctg Phe Ile Gly Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu 20 25 30	194
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ctg gtg cac ttc ata gct ttt tat cta ata ttt ctc aac atg cct gga Leu Val His Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly	290
gat gcc ccg att gct cct gtt aaa gga act gac agc agt gct tac atc Asp Ala Pro Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile	338
70 75 80 aaa tcc agc aaa raa ttt gcc att ctc tgc akt ttt ctg tkg ggc ctt Lys Ser Ser Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu	386

85	90	95	
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Gly Asn Ser Cys Phe Asn			
	105 110		
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Tyr Ser Glu Xaa Ser Ala	Pro Xaa Phe Ala Ile Phe	Asn Phe Val Gln	
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His Trp Gln Leu Leu Val	Met Val Ile Phe Gly Phe	Xaa Gly Thr Ile	
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Ser Phe Phe Thr Val Glu	Trp Glu Xaa Ala Ala Phe	Val Xaa Arg Gly	
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Ser Asp Tyr Arg Ser Ile			
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aat aag too tat aag aat aaa ga Asn Lys Ser Tyr Lys Asn Lys As -70	p Ser Val Arg Ile							
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Ser His Ala His Trp Xaa Ser Xaa
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Thr	Glv	Pro	Trp	Gly	Ala	Val	Ala	Thr	Ser	Ala	Gly	Gly	Glu	Glu	Ser	
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Leu	Lvs	Cvs	Glu	Asp	Leu	Lys	Val	Gly	Gln	Tyr	Ile	Cys	Lys	Asp	Pro	
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Ile	Pro	Cvs	Phe	Glv	Phe	Val	Lys	Xaa	Xaa	His	Cys	Arg	Val	Xaa	Trp	
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Pro Lys Leu Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile -25 -20 -15	
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Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser Ser
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                        -15
                                             -10
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Pro Phe Leu Trp Lys Leu
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ctggcccccc atagcaccca gtgcatcctt tttacaagtg gaagaactag g atg gct Met Ala	237
ttc caa agt ctt cta gaa atg aag ttc ttt ctc tgt gca gct ttc ccc	285
Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala Phe Pro	
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Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly Lys Pro	
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Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg Ile Trp	
15 20 25	
cct tagcttctgg gcctatcsgc tgccttccct cttyttccta ccacctcttc	434
Pro	404
tgccttcctt trawctctgt tgggcttggg gatcttagtt ttcttttgtt tatttcccat	494 554
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agagcaagtg gaatctctaa ga atg gct tcc agc cac tgg aat gaa acc act	1/2
Met Ala Ser Ser His Trp Asn Glu Thr Thr -45 -40	
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acc tot gtt tat cag tac out ggt ttt caa gtt caa aaa att tac cot	220
Thr Ser Val Tyr Gln Tyr Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro	
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Phe His Asp Asn Trp Asn Thr Ala Cys Phe Val Ile Leu Leu Phe	200
-20 -15 -10	
ata ttt aca gtg gta tct tta gtg gtg ctg gct ttc ctt tat gaa gtg	316
Ile Phe Thr Val Val Ser Leu Val Val Leu Ala Phe Leu Tyr Glu Val	
-5 1 5 10	
ctt gam wgc tgc tgc tgt gta aaa aac aaa acc gtg aaa gac ttg aaa	364
Leu Xaa Xaa Cys Cys Cys Val Lys Asn Lys Thr Val Lys Asp Leu Lys	
aca mad mad ofo cho cho tan all them all the tan all the are	

733

772

15 20 25	
agt gaa ccc aac cct ctt ara akt atg atg gac aac atc aga aaa cgt	412
Ser Glu Pro Asn Pro Leu Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg	***
30 35 40	
gaa act gaa gtg gtc taacactcta taraaaatga acaaaatctc tgaaagcagc	467
Glu Thr Glu Val Val	
45	
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tgactgaatg gttaaaacat ttctagtara aggggaaaaa aaakttaaac atgcactgtt	587
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cactteetga gtgageteae ttacetteee tgaatggtga gge atg gat gaa tat	295
Met Asp Glu Tyr	
-30	
tcc tgg tgg tgc cac gtg tta gag gtg gta aag ggt caa atg ttt act	343
Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly Gln Met Phe Thr	
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Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys Gln Arg Phe Phe	
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Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser Thr Val Thr Pro	439
5 10 15 20	
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Ser Trp Arg Leu Cys Leu Val Ser	
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Gaggeteeta ettrogete chaaagtget gagattacag gegtgagee cegeacegg	673

gageeteetg etttegeete etaaagtget gggattacag gegtgageea eegeaceegg

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   Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp
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                               -75
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Phe His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala
        -65
                            -60
                                                -55
gga gtg agc ctt cca gga att ttg gct gcc aaa tgt ggt gca gaa gta
                                                                      203
Gly Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val
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                                                                      251
Ile Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg
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                                        -25
caa agc tgc caa atg aat aac ctg cca cat ctg cag gtg gta gga cta
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Gln Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu
                                    -10
aca tgg ggt cat ata tct tgg gat ctt ctg gct cta cca cca caa gat
                                                                      347
Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
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att atc ctt gca tct gat gtg ttc ttt gaa cca gaa rat ttt gaa gac
                                                                      395
Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp
                        20
att ttg gct aca ata tat ttt ttg atg cac aar aat ccc aag gtc caa
                                                                      443
Ile Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln
                    35
                                        40
ttg tgg tct act tat caa gtt agg art gct gac tgg tca ctt gaa gct
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Leu Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala
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tta ctc tac aaa tgg gat atg aaa tgt gtc cac att cct ctt gag tct
                                                                      539
Leu Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser
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                                70
ttt gat gca gac aaa gaa rat ata gca gaa tct acc ctt cca gga aga
                                                                      587
Phe Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg
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                                                90
cat aca gtt gaa atg ctg gtc att tcc ttt gca aag gac agt ctc
                                                                      632
His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
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                        100
                                            105
tgaattatac ctacaacctg ttctgggaca gtatcaatac tgatgagcaa cctggcacac
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gtg cag aac ccc ggc gcg gcc ctt gac ctt tgc att gca gct gta att Val Gln Asn Pro Gly Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile -30 -25 -20	149
aaa gaa tgc cat ctc gtc ata ctg tcg ctg aag agc caa acc tta gat Lys Glu Cys His Leu Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp -15 -10 -5	197
gca gaa aca gat gtg tta tgt gca gtc ctt tac agc aat cac aac aga Ala Glu Thr Asp Val Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg 1 5 10	245
atg ggc cgc cac aaa ccc cat ttg gcc ctc aaa cag gtt gag caa tgt Met Gly Arg His Lys Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys 20 25 30	293
tta aag cgt ttg aaa aac atg aat ttg gag ggc tca att caa gac ctg Leu Lys Arg Leu Lys Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu 35 40 45	341
ttt gag ttg ttt tct tcc aag taagtaagtg gtccarttgc tttgtgatgt Phe Glu Leu Phe Ser Ser Lys 50	392
ggtgggctgg gaactcaatg tcttgtgatc kcccttwgga ttkctctakg ctygckgttg gaatataacc aattataccw cagctgtaka aatwttgttt taatgtgggg taccyggtgt ktgtggtaat cttctgacat tgatctatgg gartgactgg tgtgacattg aaatctgggt catggtagat tatattaaaa catcagtggg ctgttattgt gcttaactac ctcaagttga gcttaaagca agtcttcact tgaaaactgc tatagaaatg ctttatatt aaaaatgaaa gtaatgggar mttgcacata gctgaaaatg tgaagggtcg cccagggagg amatggaagc tctgtgcttc ttctgccata ccttgcccta tgcatctct tgttcaatc ctttgtcata	452 512 572 632 692 752 812
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tee eec cag gee etg gag gae teg gge eeg gtg aat ate tea gte tea
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Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
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                             -90
                                                 -85
atc acc cta acc ctg gac cca ctg aaa ccc ttc..gga ggg tat tcc cgc
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Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
                         -75
                                             -70
aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
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Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
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                                         -55
tca ggc agg gaa gcc cac gag gag ata aac atc acc ttc acc ctg cct
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Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
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                                     -40
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Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
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                                                                       341
Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
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                                                 -5
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Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
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cca cgc tct ggt aca aga tct tca caa ctg cca gag atg cca aca caa
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Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
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aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
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gaa aag tot ato atg ott taaatoocaa gottacagtg attgttocag
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Glu Lys Ser Ile Met Leu
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gcaatcctga attttgtccc gagaaggtgg ctttggctga agcctaattc cacagctcct
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1073

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                                          -10
caa agg cca gag tca cag gaa gga ctt ctt cca ggg aga tta gtg gtg
                                                                    96
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
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Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
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Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
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Leu Arg Met
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Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp Thr Arg Gln Leu Pro Leu
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                         -20
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Leu Thr Ser Ala Leu His Gly Leu Gln Gln Gln His Pro Ala Phe Ser
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                                        1
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Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
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gag ggt ttc gct gat gag agc ctg gat ctg gtg gcc gct gcc ctt ttc
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Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
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Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe
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ctt cga ttc ctt ttc ttg gta tca acg ttt gat tgg aag aac aac ccc
                                                                      344
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Leu Phe Val Asn Leu Asn Asn Glu Leu Thr Val Glu Glu Gln Val Glu
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Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala Gln Leu Pro Val Met Val
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Pro Ser Ala Gln Ile Leu Gln Gln Leu Val Val Leu Ala Ala Glu Xaa
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ctg ccc atg tta rar aas cag ctc atg gat ccc cgg gga cct ggg gac
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Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp Pro Arg Gly Pro Gly Asp
                    140
                                        145
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Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp Ile Tyr Asp Val Leu Ile
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cgc ctg tct cct cgc cat atc ccg cgg cac cgc cag gct gtg gac tcr
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Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
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158

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with the geg the contraction contraction that contract contraction	257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile	
25 30 35	
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 Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
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 Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser Asp
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 age gat gaa tta get tea ggg ttt ttt gtg tte eet tae eea tat eea
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 Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
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Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	
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Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser	
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His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	319
nie oin oin the by his had bor the bor the bor the	319
-15 -10 -5	319
-15 -10 -5	319 367
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-15 -10 -5  ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	

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140

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seq KMLISVAMLGAXA/GV

<sup>&</sup>lt;211> 628

<sup>&</sup>lt;212> DNA

TONE CONTINUES (SEE A MARIO 2019) (SEE A MARIO 2019

<221> polyA\_signal <222> 595..600 <221> polyA site <222> 618..627 <400> 292 aagtgagacc gegeggeaac agettgegge tgeggggage teccqtqqqc qetecqetqq 60 ctgtgcaggc ggcc atg gat tcc ttg cgg aaa atg ctg atc tca gtc gca Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala -15 -10 atg ctg ggc gca rgg gct ggc gtg ggc tac gcg ctc ctc gtt atc gtg 158 Met Leu Gly Ala Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val -5 1 acc ccg gga gag cgg cgg aag cag gaa atg cta aag gag atg cca ctg 206 Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu 15 254 Gln Asp Pro Arg Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu. 30 ctg gcc act ctg cag gag gca gcg acc acg cag gag aac gtg gcc tgg 302 Leu Ala Thr Leu Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp 50 agg aag aac tgg atg gtt ggc ggc gaa ggc ggc gcc acg gga kgt cac 350 Arg Lys Asn Trp Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His 65 cgt gag acc gga ctt gcc tcc gtg ggc gcc gga cct tgg ctt ggg cgc 398 Arg Glu Thr Gly Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg 80 85 . agg aat ccg agg cag ctt tct cct tcg tgg gcc can cgg aaa atc cgg Arg Asn Pro Arg Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg 95 100 amc gaa aat wcc atg cca gga ctc tcc ggg gtc ctg tgaactgccg 492 Xaa Glu Asn Xaa Met Pro Gly Leu Ser Gly Val Leu 115 tegggtgage acgtgteece caaaccetgg actgactget ttaaggteeg caaggeggge 552 cagggccgag acgcgagtcg gatgtggtga actgaaagaa ccaataaaat catgttcctc 612 cammcaaaaa aaaaah 628

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<222> 50..631

<221> sig\_peptide

<222> 50..244

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<222> 777..782

<221> polyA\_site

<222> 801..812

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gct ccc ctg agc tgc ctg tca ccg act aag tgg agc agt gtt tct tcc  Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser Val Ser Ser  -60  -50	06
Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr Arg Asn Leu  -45  -40  -35	54
cct ttt cag ttc tgt ctc cgg cag gct ttg agg atg aag gct gcg ggc Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys Ala Ala Gly -30 -25 -20 -15	02
att ctg acc ctc att ggc tgc ctg gtc aca ggc gtc gag tcc aaa atc  Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu Ser Lys Ile  -10  -5	50
tac act cgt tgc aaa ctg gca aaa ata ttc tcg agg gct ggc ctg gac  Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala Gly Leu Asp  5 10 15	98
aat cyg agg ggc ttc agc ctt gga aac tgg atc tgc atg gcg tat tat  Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met Ala Tyr Tyr  20  30	46
gag agc ggc tac aac acc aca gcc car acg gtc ctg gat gac ggc agc Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser 35 40 45 50	94
atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc  Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg  55  60  65	42
gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu 70 75 80	90
rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt 53 Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val 85 90 95	38
aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt 58 Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys 100 105 110	86
gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc 63 Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser 115 120 125	31
taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc 69	91
5 5	51
3 · · · · · · · · · · · · · · · · · · ·	11 13

<210> 294

<211> 778 <212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 154..576

<221> sig\_peptide

<222> 154..360

<223> Von Heijne matrix score 4.80000019073486 seq MMVLSLGIILASA/SF

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                                                                       120
ctggaaccaa cgggcacagt tggcaacacc atc atg aca tca caa cct gtt ccc
                                                                       174
                                      Met Thr Ser Gln Pro Val Pro
                                                      -65
aat gag acc atc ata gtg ctc cca tca'aat gtc atc aac ttc tcc caa
                                                                       222
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln
                             -55
gca gag aaa ccc gaa ccc acc aac cag ggg cag gat agc ctg aag aaa
                                                                      270
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys
                                             -35
cat cta cac gca gaa atc aaa gtt att ggg act atc cag atc ttg tgt
                                                                      318
His Leu His Ala Glu Ile Lys Val Ile Gly Thr Ile Gln Ile Leu Cys
                    -25
                                         -20
ggc atg atg gta ttg agc ttg ggg atc att ttg gca tct gct tcc ttc
                                                                      366
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe
                -10
                                    -5
tet eca aat tit ace caa gig act tet aca etg tig aac tet get tae
                                                                      414
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr
                            10
cca ttc ata gga ccc ttt ttt gtr akt aaa btt tct gag gag ggc agg
                                                                      462
Pro Phe Ile Gly Pro Phe Phe Val Xaa Lys Xaa Ser Glu Glu Gly Arg
                        25
                                            30
atg ggg caa ara ggg gag gaa rat vcc aat agc tta aac ttc cca sct
                                                                      510
Met Gly Gln Xaa Gly Glu Glu Xaa Xaa Asn Ser Leu Asn Phe Pro Xaa
                    40
                                        45
gcc agc ttg cta tkt ttg atc tgc cag gav caa gga ttc aac ggt gaa
                                                                      558
Ala Ser Leu Leu Xaa Leu Ile Cys Gln Xaa Gln Gly Phe Asn Gly Glu
                                    60
tot tgt tot cot gtc ggg targataaca ggggttgctt rattttagat
                                                                      606
Ser Cys Ser Pro Val Gly
            70
caatttctta tcagactcaa ataaacattt cttttgaaaa tcatcttatt cttcacatta
                                                                      666
tcatcttgag ctatgatgga aactagtgas ktctctccag gtttaggcga aaaaaaaatc
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catgaattag gataaagttg ggaaggaaca ttttatacaa aaaaaaaaah cc
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<211> 1060

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<222> 154..897

<221> sig\_peptide

<222> 154..360

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seq MMVLSLGIILASA/SF

<221> polyA\_signal

<222> 1017..1022

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<221> polyA\_site <222> 1044..1054

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agtaaaaaaa cactggaata aggaagggct gatgactt aaccgttgat gggactgaga aaccagagtk aaaacct	ett togagettet gaggaeteag 120
ctggaaccaa cgggcacagt tggcaacacc atc atg	aca toa caa cot gtt coc 174
	Thr Ser Gln Pro Val Pro
	-65
aat gag acc atc ata gtg ctc cca tca aat g	gtc atc aac ttc tcc caa 222
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn V	Val Ile Asn Phe Ser Gln
-60 -55	-50
gca gag aaa ccc gaa ccc acc aac cag ggg (	cag gat agc ctg aag aaa 270
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly (	
-45 -40	-35 act atc cag atc ttg tgt 318
cat cta cac gca gar rtc aaa gtt att ggg a His Leu His Ala Glu Xaa Lys Val Ile Gly 7	
· · · · · · · · · · · · · · · · · · ·	-20 -15
ggc atg atg gta ttg agc ttg ggg atc att t	
Gly Met Met Val Leu Ser Leu Gly Ile Ile I	
-10 -5	1
tot coa aat ttt acc caa gtg act tot aca	
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr 1	Leu Leu Asn Ser Ala Tyr
5 . 10	15
cca ttc ata gga ccc ttt ttt ttt atc atc	
Pro Phe Ile Gly Pro Phe Phe Ile Ile S	
20 25	30 gtg cat acc acc ctg gtt 510
gcc aca aaa aaa agg tta acc aac ctt ttg g Ala Thr Lys Lys Arg Leu Thr Asn Leu Leu V	
	45 50
gga age att etg agt get etg tet gee etg	
Gly Ser Ile Leu Ser Ala Leu Ser Ala Leu	Val Gly Phe Ile Xaa Leu
55 60	65
tot gto aaa cag goo acc tta aat cot goo	tca ctg cak tgt gag ttg 606
Ser Val Lys Gln Ala Thr Leu Asn Pro Ala	
70 75	80
gmc aaa aat aat ata cca aca ara akt tat g	
Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa Tyr Y 85 90	val kaa Tyr Phe Tyr HIS 95
gat toa ctt tat acc acg gac kgc tat aca	
Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr Thr	
100 105	110
gga act ctc tct ctg atg ctg att tgc act	ctg ctg gaa ttc tgc cwa 750
Gly Thr Leu Ser Leu Met Leu Ile Cys Thr	
	125 130
set gtg ete act get gtg etg egg tgg aaa	
Xaa Val Leu Thr Ala Val Leu Arg Trp Lys	
135 140	145. tac att ggw aat tot ggm 846
cct ggg agt gta ctt ttc ctg cct cam agt Pro Gly Ser Val Leu Phe Leu Pro Xaa Ser	
150 155	160
atg tcc tca aaa atg acy cat gac tgt gga	
Met Ser Ser Lys Met Thr His Asp Cys Gly	
165 170	175
tct taagaaaaaa gggagaaata ttaatcagaa agt	tgattct tatgataata 947
Ser	
tggaaaagtt aaccattata gaaaagcaaa gcttgag	
gtaatgaaca ttaaaaaaaa ccattatttc actgtca	aaa aaaaaaamcc nkt 1060

The state of the s

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<222> 146..253
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gtgtcggacc tctagagcta atctcactag atgtgagcca ttgtttatat tctagccatc
                                                                  172
ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                          Met Gln Val Pro His Leu Arg Val Trp
                               -35
                                                  -30
                                                                  220
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg. Asn Leu Gly Phe Thr
        -25
                           -20
agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                  268
Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                       -5
                                          1
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
                                                                  322
Lys Lys Arg Lys Leu Xaa Leu Phe
               10
                                                                  382
tattgttgtt ttgctttttc tgccttcaaa ctactcccac aggccaaata tavctggctg
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444
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-215-

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<222> 726..731

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<222> 743..754

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ttttg atg gtg gcc ctg aac ctc att ctg gtt ccc tgc tgc gct tgg	170
Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp	
-10 -5 1	
tgt gac cca cgg agg atc cac tcc cag gat gac gtg ctc cgt agc tct	218
Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser	
5 10 15	
get get gat act ggg tet geg atg eag egg egt gag gee tgg get ggt	266
Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly	_ • -
20 25 30	
tgg aga agg tca caa ccc ttc tct gtt ggt ctg cct tct gct gaa aga	314
	214
Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg	
35 40 45	2.50
ctc gag aac caa cca ggg aag ctg tcc tgg agg tcc ctg gtc gga gag	362
Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu	
50 55 60 65	
gga cat aga atc tgt gac ctc tgacrrctgt gaasccaccc tgggctacar	413
Gly His Arg Ile Cys Asp Leu	
70	
aaaccacagt cttcccagca attattacaa ttcttgaatt ccttggggat tttttactgc	473
cctttcaaag cacttaaktg tkrratctaa cgtkttccag tgtctgtctg aggtgactta	533
aaaaatcaga acaaaacttc tattatccag agtcatggga gagtacaccc tttccaggaa	593
	653
taatgttttg ggaaacactg aaatgaaatc ttcccagtat tataaattgt gtatttaaaa	
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2222 0037	
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totoc atg acc cgg ctc tgc tta ccc aga ccc gaa gca cgt gag gat ccg	110
Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro	
-55 -50 -45	
atc cca gtt cct cca agg ggc ctg ggt gct ggg gag ggg tca ggt agt	158
Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser	
-40 -35 -30	
cca gtg cgt cca cct gta tcc acc tgg ggc cct agc tgg gcc cag ctc	206
Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu	

-25 -20 -15	
ctg gac agt gtc cta tgg ctg ggg gca cta gga ctg aca atc cag gca Leu Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala	254
-10 -5 1 5 gtc ttt tcc acc act ggc cca gcc ctg ctg ctg ctt ctg gtc agc ttc	302
Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe 10 15 20	302
ctc acc ttt gac ctg ctc cat agg ccc gca gtc aca ctc tgc cac agc	350
Leu Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser 25 30 35	
gca aac ttc tca cca ggg gcc aga gtc agg ggg ccg gtg aag gtc ctg Ala Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu 40 45	398
gac age agg etc tac tec tge aaa tgg gta eag tet eag gac aac	446
Asp Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn 55 60 65	
tta gcc tcc agg aag cac tgc tgc tgc tca tgg ggc tgg gcc cgc Leu Ala Ser Arg Lys His Cys Cys Cys Ser Trp Gly Trp Ala Arg	494
70 75 80 85	
tcc tgaaaacctg tggcatgccc ttgwaccctg cttggcctgg ctttctgcct Ser	547
ccatccttgg gcctgakanc ccctccccac aactcagtgt ccttcaaata tacaatgacc acccttcttc aaaaaaaaaa	607 629
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-15 ctc gtc cta acc ctg tgc acc ctc ccg ctg gct gtg gcg tct gct ggc	105
Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly -10 -5	103
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys	153
5 10 15	
gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp	201
20 25 30 35	
caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt agt gag tcy ccc Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser Glu Ser Pro	249

40 45 50	
ccg ggc aga ggg cas gtg cca bgt gcc ggg gaa kgg ccg gtg ccc ccg Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro Val Pro Pro 55 60 65	297
	215
cct ctc wkc gac tta bct atg act cct cgg ckc ycc agg gcc tgg ggc Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg Ala Trp Gly 70 75 80	345
cck gtg ggt ccd aaa gtg cct cct gct gtc tct ccc gcg ctg ggc tcg	393
Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala Leu Gly Ser 85 90 95	
ggc gag cat ccs rva btg tgaatkkkga cttttttctc ckccatttga	441
Gly Glu His Pro Xaa Xaa 100 105	
	501
agtgtcacta ggaactgtca gcaggacaaa ggctctgatg tcactgaatt tacaaaraca gcaggaacrs ackggtgggg atgggcagct gttcrargcr atgggtkatc tgcccttcct	561
ggcacagcac artacacctg ccatacaacc carcatcagg cakgctgcac tggaatcgat	621
acagtgtatg acaatgtcat atagtataac acaacataat gaatataacg tgtatattgc	681
aacttaatat aatacgatgt aatataatgc tacataatac aacataatat aataaaatag	741
aatgcaacac aaaaaaaaa aacc	765
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Met Glu Arg	
-15	
ctc gtc cta acc ctg tgc acc ctc ccg ctg gct gtg gcg tct gct ggc	105
Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly	
-10 -5 1	3.53
tgc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag	153
Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys 5 10 15	
gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac	201
Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp	201
20 25 30 35	
caa gtc tgc atc tcc aac gag gtg gtc gtc tct ttt aaa tgg agt gta	249
Gln Val Cys Ile Ser Asn Glu Val Val Ser Phe Lys Trp Ser Val	- 1.5
40 45 50	
cgc gtc ctg ctc agc aaa cgc tgt gct ccc aga tgt ccc aac gac aac	
	297
Arg Val Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn	297

atg aak ttc gaa tgg tcg co			345
Met Xaa Phe Glu Trp Ser Pr	75	80	-
agg cgc tgc tgt tcc tgg go	t ctc tgc aac agg	gca ctg acc cca cag	393
Arg Arg Cys Cys Ser Trp Al			
. 85		95	
gag ggg cgc tgg gcc ctg ci			441
Glu Gly Arg Trp Ala Leu Xa		•	
100 105	110	115	489
agg ggc ara aaa acc tgg gt Arg Gly Xaa Lys Thr Trp Va			407
120	125	130	
ctt ccc awt tcc aac ccc ct			534
Leu Pro Xaa Ser Asn Pro Le			
135	140	145	
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taaactctca tgcccccaaa aaaa	ıaaaaa		623
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Gly Glu His His Ser	
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5 10 15	
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Val Pro Arg Arg Ala Gly	
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                            -10
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Gly Gly Val Asn Lys Ile Ala Glu Lys Ile Cys Gly Asp Leu Lys Asp
ccc tgc aaa ttg gac atg aat ttt gga agc tgc tat gaa gtt cac ttt
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Pro Cys Lys Leu Asp Met Asn Phe Gly Ser Cys Tyr Glu Val His Phe
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Glu Val Xaa Cys Val Ala Lys Tyr Lys Pro Pro Arg
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														Phe		311
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His	Tyr	Arg	Cys	Ser	Asn	His	Val	Tyr	Tyr	Ala	Lys	Arg	Val	Leu	Cys	
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Ser		Pro	Val	Ser	Ile		Ser	Pro	Asn	Thr		Lys	Glu	Ile	Glu	
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												Leu				
				135				•	140							
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ggag	gcaa	gcg (	ccaga	agca	ca a	gcag	gagca	a ag	gagt	ggag	caca	aggc	agg .	agcc	gacaca	647
_		_		•		-				_	_				agagga	707
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		-	-	_		-			-	-					gctcat	887
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Arg Val Ser Ser Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu	,

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acc	ccc Pro		Ser														253
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	agt Ser																397
	gag Glu								Ser					Met	cca		445
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	gtc Val					cac					att						637
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	cgt Arg			gga					ctg					ttt			733
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Met Val Cys Leu Phe Phe Arg Leu Ile Phe Ser Glu His Leu Pro Ile	
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Thr Ser Ala Gly	
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                                   -30
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 Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala
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5 10 15	
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Val Ile Pro Ser Ala Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu	
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Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser	_ <b>_</b> .
15 20 25	
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acc Thr	gar Glu	agc Ser	tcc Ser 190	tcc Ser	cac His	tcc Ser	agg Arg	ctg Leu 195	tcc Ser	ccc Pro	cga Arg	aar Lys	amm Xaa 200	cac	tta Leu	785
ctg Leu	tac Tyr	atc Ile 205	ctc Leu	arg Xaa	ccc Pro	tct Ser	cgg Arg 210	cag	ctg Leu	targ	iggt <u>c</u>	199 9		iggga	ir	835
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agt aaa tgc tgt aaa ggt ggt cca gat gaa gat gca gta gaa aga cag Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu Arg Gln -55 -50 -45	105
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Met Asn	
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Pro Cys Ash Leu His Cys Ser Trp Leu His Ser Ser Pro Arg Pro Asp	303
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Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro His Pro	
. 10 15 20	
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Cys Ala Thr Tyr Pro Pro Xaa	200
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Leu Leu Thr Tro Leu Phe Thr Leu Lou Phe Tro Leu Leu Phe Tro Leu Ph	222
Leu Leu Thr Trp Leu Phe Thr Leu Leu Phe Leu Ile Met Leu Val Leu -15	
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Lys Leu Asp Glu Lys Ala Pro Trp Asn Trp Phe Leu Ile Phe Ile Pro	
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Met	
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Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser Ser	
-15 -10 -5	221
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Ile Ile Leu Met Lys	• • •
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                    -20
                                         -15
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Ser Cys Leu Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala
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Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
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Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
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Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
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Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr Asp Gly Ile Phe  10 15 20  tat gaa ttt cgt tct tat tac ctt aag ccc tca aag atg aat gag ttc Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys Met Asn Glu Phe 25 25 26 27 28 29 29 20 20 20 20 20 20 20 20 20 20 20 20 20	200 248 296 344
Met         Cys         Ser         Ser         Phe         Ala         Thr         Gly         Pro         Arg         Gln         Tyr         Asp         Gly         Ile         Phe           tat         gaa         ttt         cgt         tct         tat         tac         ctt         aag         ccc         tca         aag         atg         aat         gag         ttc           Tyr         Glu         Phe         Arg         Arg         Thr         Arg         Arg         Thr         Ala         His         Ser         Glu         Phe         Arg         Arg         Thr         Ala         His         Ser         Glu         Phe         Arg         Thr         Ala         His         Ser         Glu         Phe         Arg         Thr         Ala         His         Ser         Glu         Arg         Thr         Ala         His         Ser         Glu         Arg         Thr         Ala         His         Arg         Thr         Ala         Arg         Arg	200 248 296 344 392

ctaggctaca caaaactagt tggagtgttc cacacagagt acggagcact caacagagtt

627

742

802

862

880

and the mid-state of the second t

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catgttcttt ggtggaatga gagtgcagat agtcgtgcag ctgggagaca taagtcccat	687.
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                                          -35
gag atg gta cag gcg ctt tac gag gct cct gct tac cat ctt att ttg
                                                                     98
Glu Met Val Gln Ala Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu
-30
                    -25
                                       -20
gaa ggg att ctg atc ctc tgg ata atc aga ctt ctt ttc tct aag act
                                                                    146
Glu Gly Ile Leu Ile Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr
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                -10
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Tyr Lys Leu Gln Glu Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu
                            10
                                               15
                                                                    242
ctg att gaa gag tgg caa cca gaa cct ctt gtt cct cct gtc cca aaa
Leu Ile Glu Glu Trp Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys
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                                          ..30
gac cat cct gct ctc aac tac aac atc gtt tca ggc cct cca agc cac
                                                                    290
Asp His Pro Ala Leu Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His
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                                       45
aaa act gtg gtg aat gga aaa gaa tgt ata aac ttc gcc tca ttt aat
                                                                    338
Lys Thr Val Val Asn Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn
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Phe Leu Gly Leu Leu Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala
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Gly Thr Phe Glu
    100
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195

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-244-

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784

844

TOTAL AS IN STANDARD FOR A MARKATER AND THE STANDARD AND AND AND A CONTRACTOR OF A STANDARD AS A STANDARD ASSA STANDARD AS A STA

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ttgagcaaaa tagtatggga cttccaagaa atg ttt tta aag tca ggg gca ggc
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                                 Met Phe Leu Lys Ser Gly Ala Gly
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Leu Ser Ser Cys Leu Leu Pro Leu Cys Trp Leu Glu Arg Lys Asp His
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Met :	Asn	Xaa	Tyr	Ala	Ser	Pro	Phe	Asn	Xaa	Gln	Leu	Xaa			Хаа	
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Ser	Tyr	Gln	Glu	Gln	Glu	Leu	${\tt Gln}$	Asp	Phe	Leu	Leu	Ser	Gln	Met	Ser	
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02				15	-				20		_			25		
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Len	Dhe	Gln	Phe	Val	Met	Agn	Len	Lvs	Val	Ala	Ala	Ara	Leu	Trp	Phe	
Deu	FIIC	45	FIIC	vai	Mec	Yob	50	טעם	•			55				
200	++~		gta	200	225	ata		acc	ttc	caa	222	_	atq	ttt	tac	442
cor	Dha	Tou	Val	Thr	λen	Val	Tare	Thr	Dhe	Gln	Lvs	Val	Met	Phe	Tvr	
Ser		Leu	Val	1111	ASII	65	nys	1111	FIIC	OIII	70	VU.			-1-	
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dal	ala Tla	mb-	Asn	994	37-3	710	Dho	77-1	990	Uie	Cor	Lve	Lve	Phe	Ser	
-	116	1111	ASII	GIA	80	116	FIIC	Vai	GIY	85	501	Lyc	_,_		90	
75			tgg	~		1000	a++	++~	+++		222	taa	arm	tac		538
gga	aca	ddd	Trp	aag	3763	Vaa	TIO	Tou	Dha	710	Lve	Trn	Yaa	Cvs	Len	
GIY	TTE	ьys	Trp		vai	Add	116	ъęи	100		цуз	ııp	nuu	105	200	
				95			+	+-+			++0	car	ato		cct	586
tgt	ctg	cac	tta	gcc	CCC	gtc	m	m	yat	Dha	200	Car	Mot	Dhe	Dro	300
Cys	Leu	His	Leu	Ala	Leu	vaı	туг			Pne	Pile	GIII	120		FIO	
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aaa	raa	gtt	tcc	ara	aac	דבנ	gac	ttg	aaa	. tgt	try	Car	Tla	) aac	Tur	034
Lys	Xaa			хаа	Asn	Pne			гъ̀х	Cys	Leu			RSH	Tyr	
		125					130					135			24.2	682
aag	cac	aaa	gaa	gar	ata	act	tcc	aaa	aga	gtg	CLG	ייי	. LLd		ata	002
Lys			Glu	Glu	Ile			. гу	Arg	vaı			ւ բես	грур	Ile	
	140					145		٠.			150			<b>.</b>	_	733
			aaa					cact	ttc	aaac	ודדד	ca c	ctta	taaa	L	/33
	Ile	Arg	Lys	Cys			:									
155					160											703
gac	aagt	gct	ttga	aatg	ca g	aagt	ttat	g ta	cagt	tgta	tat	acag	tat	gaca	agatgt	793
aaa	ataa	tat	gttt	ttca	tg c	agtt	taaa	ıa ta	ittac	taac	: tta	aggg	ittt	ctat	gtgctt	853
ttt	aaaa	tat	tcct	tctt	tg a	tgtt	gaca	it ca	laata	aagt	ato	tggt	tta	aaaa	aaaaaa	913
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-247-

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<222> 672..752

Borne Control (1) of the first of the March March Control Cont

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                                                                      120
cttatagtat gcatatattc agcatatgtt gcatgtsttc agaattacat aagatgaaat
                                                                      180
ccctttcatt gcaacttgca agtgagaaaa gatccttagt ggctctggtg gaagaaatag
                                                                      240
                                                                      300
tatttettet teteagggtg tetecetgee ttggeceete ecagaageee eggetttaaa
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agtgaaaatg tttgaaacat gaaacatgtc tgtaggaagc atcagcatgg ccataagtgc
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artgattttc atatatgcct ctgcccattt caaatatatt tttgacatga ataaatctaa
cagtatacar aataattcat gtaaraccct aacgtgtaca tgtgaaaaag catttctata
                                                                      480
taatgtgagg agcactggcc atcaattagg gaaataaagg tcatgtaata ttgcaaattt
                                                                      540
tcaaaataga gcsstgcaag ataactgcaa tcataccaaa aactatttga gtaaatggat
                                                                      600
ttttaaagta atttttgttt aaaaaaattt atatttcaga agsagaaaat gtcaaatgat
                                                                      660
agtetttgta a atg gtg gtg cac ett ete tat gea eat etg tet ttt aca
                                                                      710
             Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr
                     -15
                                                                      752
tca aaa aga gct gtg gtc atg cta aaa tta gag ata act ttt
Ser Lys Arg Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe
                                5
                1
tgaatgactt ggtcaagctg tgtgtaaaat atttaaccat aagtcaagta cagtgtacta
                                                                      812
                                                                      872
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tttatgtctt ctggtatttg attttgaatg ttttttaagt cagtggtgcc tttaggcaag
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aactttcgaa attaatcatt ctttgtgttt tctgattttt caggtaacat gtacactatt
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tagaaaccat catagtttat tcaccttaaa aaattgattg tattatttaa atatatcact
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tagatgggca tttcctataa ttaggatatt ccaaatagtt gctgaaatca attgtgccat
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tgaccaatgg atgcacttgg ttagccttaa ttttttyaaa aaaaaaaaa
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Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu Phe	
-20 -15 -10 ctc cca cat tac att gaa act ttc aag cct cag tcg aaa cat tgc ttc	155
Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys Phe	
-5 1 5	
tto tgg ata gca gcc tto ttg aca tcc ctc ctc act ccc cag tcc cta	203
Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser Leu	
10 15 20 25	253
cag ggc ttc cat agc tct tta tgt gca ctt cga tcc cag cat ttt cca	251
Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe Pro	
30 35 40 tcg act tgt aat tgt ttc tgc tac ctg aca atc atc gcc ttg drd tac	299
Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa Tyr	
45 50 55	
tgg gac aac ctt tgattactca ttatatcctc aataaatatt tgttgaacca	351
Trp Asp Asn Leu	
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ttataaccgt ctttccctt atg cta agg ata gcc ctt aca ctc atc cca tct  Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser	112
-15 -10	
atg ctg tca agg gct gct ggt tgg tgc tgg tac aag gag ccc act cag	160
Met Leu Ser Arg Ala Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln	
-5 1 5 10	
cag tit tot tac cit tgc citg ccc tgc cit tca tgg aat aar aaa ggc	208
Gln Phe Ser Tyr Leu Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly	
15 20 25	
aac gtt ttg cag ctt cca aat ttc tgaaraaact aatctcarat tggcagttaa	262
Asn Val Leu Gln Leu Pro Asn Phe	
30 35	
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ctttttattt ttaatgtctt gactcttcar agttcgtacc tcaaaaraac aatgaraac	a 382
tttgctttgc tttctgctga atccctaatc tcaacaatct atacctggac tgtccagtt	c 442
tectectgtg ctatetete ttetatecaa gtaraatgta ygecaggare teetteete	c 502 t 562
tarcaatttc tactaaaatg tocaagtara atgtttcctt ttacaatcaa attactgta	362

PCT/IB98/02122 .

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seq ILSTVTALTFARA/LD

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marin and

	_			-	
	-5		1	5 ca tca ggg gct '	296
				ro Ser Gly Ala	250
10	ora Dea Cyo	15		0	
ggg ctc act	gtg gcc cca	ccc caa gcc	gtc agc ctc c	ag ggw atc tac	344
				In Gly Ile Tyr	
25		30	35		
				cc cta rgg gna	392
		Gln Leu Phe		la Leu Xaa Xaa	
40	45	tat ata tat	50	55 or too car	440
				ct tca tcc cat Ser Ser Ser His	330
Xaa GIII GIII	60	ser hed ser	65	70	
act cor rat		tgc acc ctg	-	tg gac cct acc	488
				al Asp Pro Thr	
	75	80	•	85	
				itc tta aaa abc	536
Arg Xaa Val	Cys Ile Asn		Pro Pro Pro I	le Leu Lys Xaa	
90		95	_	.00	
				at gct ggg caa	584
	Pro Tyr Pro	-	-	lis Ala Gly Gln	
105		110	115	cg ttccagggta	640
Val Asn	caattta tyta	caggia clagi	cciac cycaccac	eg ccccagggca	040
120					
	aaqtatctca a	aaaggcaac at	qqqccqaq cqcaq	tggct cacgcctgta	700
				tggag ttcaagacca	760
				ttrgc caggtgtggt	820
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aggaacrtca ta atg rwn	nnk ttc aca gac ccc tct tca	gtg aat gaa aag 171	
Met Xaa	Xaa Phe Thr Asp Pro Ser Ser V	_	
-70	-65	-60	
aag agg agg gag cgg g	aa gaa agg cag aat att gtc ctg	g tgg aga cag 219	
Lys Arg Arg Glu Arg G	lu Glu Arg Gln Asn Ile Val Let	ı Trp Arg Gln	
-55	-50	-45	
ccq ctc att acc ttq c	ag tat tit tot otg gaa atc oti	t gta atc ttg 267	

1.39

		-40					-35					-30	Val		•		
aag	gaa	tgg	acc	tca	aaa	tta	tgġ	cat	cgt	caa	agc	att	gtg	gtg	tct	31	5
Lys	Glu -25	Trp	Thr	Ser	Lys	Leu -20	Trp	His	Arg	Gln	Ser	Ile	Val	Val	Ser		
+++		cta	cta	ctt	act		ctt	ata	act	acq		tat	gtt	gaa	gga	36	3
Phe	Leu	Leu	Leu	Leu	Ala	Gly	Leu	Ile	Āla	Thr	Tyr	Tyr	Val	Glu	Gly		
-10					-5	•				1 .	-	_		5			
gtg	cat	caa	cag	tat	gtg	caa	cgt	ata	gag	aaa	cag	ttt	ctt	ttg	tat	41	1
Val	His	Gln	Gln 10	Tyr	Val	Gln	Arg	Ile 15	Glu	Lys	Gln	Phe	Leu 20	Leu	Tyr		
gcc	tac	tgg	ata	ggc	tta	gga	att	ttg	tct	tct	gtt	999	ctt	gga	aca	45	9
Ala	Tyr		Ile	Gly	Leu	Gly		Leu	Ser	Ser	Val	Gly 35	Leu	Gly	Thr		
		25					30	a+a	cat	GG2	ant		acc	tca	att	50	7
999	ctg	cac	acc The	Dho	CEG	Lou	Tur	Len	Glv	Dro	His	Tle	gcc Ala	Ser	Val	•	
Gly	40	nis	1111	FIIC	пец	45	ı yı	шсч			50						
aca		act	act	tat	σaa		aat	tca	qtt	aat	ttt	ccc	gaa	cca	ccc	55	5
Thr	Leu	Ala	Ala	Tyr	Glu	Cys	Asn	Ser	Val	Asn	Phe	Pro	Glu	Pro	Pro		
55				•	60	•				65					70		
tat	cct	gat	cag	att	att	tgt	cca	gat	gaa	gag	ggc	act	gaa	gga	acc	60	3
Tyr	Pro	Asp	Gln		Ile	Cys	Pro	Asp		Glu	Gly	Thr	Glu		Thr		
				75					80			~~~	~~~	85 tac	ato	65	. 1
att	tct	ttg	tgg	agt	atc	atc	Cox	aaa	yet	agg	TIA	Glu	gcc Ala	Cvs	Met	0,5	_
тте	Ser	ьеи	90	Ser	116	116	261	95	Val	Arg	110	Olu	100	Q <sub>1</sub> U			
taa	aat	atc		aca	qca	atc	gga		ctg	cct	cca	tat	ttc	atg	gcc	69	9
Trp	Gly	Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro	Tyr	Phe	Met	Ala		
_	_	105					110					115					_
aga	gca	gct	cgc	ctc	tca	ggt	gct	gaa	cca	gat	gat	gaa	gag	tat	cag	74	17
Arg			Arg	Leu	Ser			Glu	Pro	Asp			Glu	Tyr	Gln		
	120					125			~~~		130		at a	2072	202	70	95
gaa	בכנ	gaa	gag	atg	ctg	gaa	cat	gca	gag	Cor	gca - NIs	Gln	Val	Ara	aca Thr	,,,	-
135		GIU	GIU	mec	140		nis	Ата	GIU	145		0111		*** 5	150		
		ata	gaa	aat			ctt	tac	tto			aaq	agg	cta	tta	84	13
Val	Glv	Ile	Glu	Asn	Arq	Thr	Leu	Tyr	Phe	Phe	Leu	Lys	Arg	Leu	Leu		
	_			155					160					165			
agg Arg		aatt	gtt	agta	gtta	ct c	tgaa	gaag	a aa	actg	ctaa	agt	aaaa	aaa	aaaaa	90	01

-253-

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cccaagaaga ctgggga atg gag aga cag tca agg gtt atg tca gaa aag	170
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys	
-35 -30	010
gat gag tat cag ttt caa cat cag gga gcg gtg gag ctg ctt gtc ttc	218
Asp Glu Tyr Gln Phe Gln His Gln Gly Ala Val Glu Leu Leu Val Phe	
-25 -20 -15	
aat ttt ttg ctc atc ctt acc att ttg aca atc tgg tta ttt aaa aat	266
Asn Phe Leu Leu Ile Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn	
-10 -5 1 5	
cat cga ttc cgc ttc ttg cat gaa act gga gga gca atg gtg tat ggc	314
His Arg Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly	
10 15 20	
ctt aya atg gga cta att tta csa tat gct aca gca cca act gat att	362
Leu Xaa Met Gly Leu Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile	
25 30 35	
gaa agt ggr rct gtc tat gac tgt gta aaa cta act ttc agt cca tca	410
Glu Ser Gly Xaa Val Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser	
40 45 50	
act ctg ctg gtt aat atc act gac caa gtt tat gar tat aaa tac aar	458
Thr Leu Leu Val Asn Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys	
55 60 65 70	
aga gaa ata agt cag cac amc atc aat cct cat cam gga aat gct ata	506
Arg Glu Ile Ser Gln His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile	
75 80 85	
ctt gaa aag atg aca ttt gat cca raa atc ttc ttc aat gtt tta ctg	554
Leu Glu Lys Met Thr Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu	
90 95 100	
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Pro Pro Ile Ile Phe His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe	
105 110 115	
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Phe Gln Asn Leu Gly Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala	
120 125 130	
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Ile Ser Cys Ile Val Ile Gly	
135 140	
ggctgtgggg tcygtgatct gtgtgaggga tctaacactt ccaggattct tgctggckgg	761
gaaaattgtc tttttttar tawatcacaw atttgtatgt tttttcwgac ttaattccac	821
ggcttckgam aaatacaagg cttcaaatca aagcaaacta waggattgct ggactttctc	881
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gcttgcagct catcataaag taaaatgtgg taccaaatgg tgaaggcaat ccagcctctg	1301
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<211> 987

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tgttaagtat tatgaaaccc tgcatatact gtaataaaat ggtggatgtg aatggacaat

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941 987

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<213> Homo sapiens

<220>

<221> CDS

<222> 372..494

<221> sig\_peptide

<222> 372..443

<223> Vor Heijne matrix

<sup>&</sup>lt;211> 748

<sup>&</sup>lt;212> DNA

والرابي والواليك للسنطري ووالهيد والوالولات الأنافي والمعاصرة والمعاطرة والمراكز والمراكز المراكز المراكز

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360 qaaatqtcta cagtcagttg tttcatctag cttgcatctt aaaacacaaa cccttcagtt 410 qctttcactt a atg cac aca ttt gcc aat gac aga ggg tta tac agg atc Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile

-20 458 ctt ctt tta cat ttc tat tgt ctg cta cgc tca tca gag tat att ttg Leu Leu Leu His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu -10 -5

ggg tac aag gtt ttg ggg gtt ttt tty ccc att ttg taactgcctt 504

1

Gly Tyr Lys Val Leu Gly Val Phe Phe Pro Ile Leu 10

564 attgaaaadt aaktgccctt ccattccagg cctcctcata ttgtacttgt ttcctgccaa 624 atctqqqqqa tcatttqtat tttaactttq taatctatgg ctctgtactg ttgaaagstc 684 tcaattctgt ggggtctcct tagtatgtat gtgacttttc atgttgcaat atcacacgat 744 gggatggccc gacttttgct cttaataaat aatctgaatg agtaagaraa aaaaaaaaa accc

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ttt ctt ttg cta gaa ggc kaa aca gag caa gtr amn cat tca gag

Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His Ser Glu -5 1 5	
aca tat tgc atg ttt caa gac aag aag tac aga gtg ggt gag aga tgg Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp 10 20	261
cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac tgc atc His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile 25	309
tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn 40 50 55	357
	: 405
tgc cca gaa gac tcc tta ccc cca gtg aac aat rwg gtg acc agc Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser	450
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agg att ctg cag tta atc ctg ctt get ctg gea aca ggg ctt gta ggg 167

Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val Gly

-15 -10 -5

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Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln

1 5 10 15

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Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly Ala 20 25 30	
20 25 . 30 acq ctc atc qcc ccc aga tgg ctc ctg aca gcc gcc cac tgc ctc aag	311
Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu Lys	211
35 40 45	
ccc cgc tac ata ktt cac ctg ggg cag cac aac ctc cag aag gag gag	359
Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu	
50 55 60	
ggc tgt gag car acc cgg aca gcc act gag tcc ttc ccc cac ccc ggc	407
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65 70 75	455
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Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met Leu	
80 85 90 95	E 0.3
gtg aak atg gma teg eea gte tee ate ace tgg get gtg ega eee ete	503
Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro Leu	
100 105 110	E E 3
acc ctc tcc tca ege tgt gtc act gct ggc acc age tgc ctc att tcc	551
Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile Ser	
115 120 125	E00
gge tgg gge age acg tee age eee cag tta ege etg eet cac ace ttg	599
Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr Leu	
130 135 140	647
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Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn Ala 145 150 155	
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Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys Ala	
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Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val Asp	
210 215 220	
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Trp Ile Gln Glu Thr Met Lys Asn Asn	
225 230	
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cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	147
cgg ggc cta cta cac agt agc aaa tgg tcg gcg gag ttg gct ttc tct Arg Gly Leu Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser 25 30 35 40	195
ctc cct gca ttg cct ctg gcc gag ctg caa ccg cct ccg cct att aca Leu Pro Ala Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr 45 50 55	243
gag gaa gat gcc cag gat atg gat gcc tat acc ctg gcc aag gcc tac Glu Glu Asp Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr 60 65 70	291
ttt gac gtt aaa gag tat gat cgg gca gca cat ttc ctg cat ggc tgc Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys 75 80 85	339
Asn Ala Arg Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val 90 95 100	387
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tta Leu	ctc Leu	ggt Gly	ggt Gly	ggc Gly -5	gga Gly	gtc Val	tac Tyr	gga Gly	agc Ser 1	cgt Arg	Phe	cgc Arg	ttc Phe 5	act Thr	ttt Phe	97
cct Pro	ggc Gly	tgt Cys 10	aga Arģ	gcg	ctt Leu	tcc Ser	ccc Pro 15	tgg Trp	cgg Arg	gtg Val	aga Arg	vtg Xaa 20	cag Gln	aga Arg	cga Arg	145
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sra Xaa	gga Gly	ctg Leu	tct Ser 155	cat	cga Arg	aat Asn	ctg Leu	ctg Leu 160	gga	gat Asp	gac Asp	acc Thr	aca Thr 165	gac Asp	tgt Cys	577
tcc Ser	ttc Phe	att Ile 170	ttc	ctg Leu	taw Xaa	att Ile	ctc Leu 175	tgt	act Thr	atg Met	tcg Ser	att Ile 180	cga	cag Gln	aac Asn	625
att Ile	cag Gln 185	aag	att Ile	ctc Leu	ggc Gly	ctt Leu 190	gcc	cct Pro	tca Ser	cga Arg	gcc Ala 195	gcc	acc Thr	aag Lys	cag Gln	673
Ala	ggt	gga Gly	ttt Phe	ctt Leu	ggc Gly	cca	cca Pro	cct Pro	cct Pro	tct Ser 210	999	aag Lys	ttc Phe	tct Ser		718
aac	tgtt	ttg	tasc	aaga	gc c	atag	gtag	c ct	tack	taga actt	999	cctc	ttt	ctag	actggc ttttga tgatag	778 838 898

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cgc ctc tgt ggt agc gag cac ccc cga aga cca cct gag cgc ccc gag Arg Leu Cys Gly Ser Glu His Pro Arg Arg Pro Pro Glu Arg Pro Glu -65 -60 -55	208
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala -50 -45 -40	256
tcg agc act gcc caa gca caa aag cct tca gtg ccc cgg agc aat ttt Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe -35 -30 -25 -20	304
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-5 1 5	
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ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag	299
	299
ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys	350
ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys 25 30 35 40 gcg agg ctg cta acc cac tgg tgagcagatg gattatgggg tccagttcac Ala Arg Leu Leu Thr His Trp	
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ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys 25 30 35 40 gcg agg ctg cta acc cac tgg tgagcagatg gattatgggg tccagttcac Ala Arg Leu Leu Thr His Trp	

acceptible Medical Contraction of the members of the Contraction of th

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530

590

650

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710
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Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
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Gly Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr
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Met Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys
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Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser
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         Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln
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Pro Leu Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr
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Gly Xaa Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu	
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gcc Ala	cta Leu	cac His 60	atg Met	ctc Leu	ttc Phe	ctg Leu	ctc Leu 65	tat	ctg Leu	cat His	ttt Phe	gcc Ala 70	tac Tyr	cac His	aaa Lys	482
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Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser Ala His Pro Pro Gln	344
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Pro His Phe Leu Lys Ser Asn Leu Phe Leu Gln Leu Leu Val Ser His	282
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379

1197

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WO 99/31236

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tgaaagavat tct atg cat ggt ttt gaa ata ata tcc ttg aaa gag gaa  Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu  -45  tca cca tta gga aag gtg agt cag ggt cct ttg ttt aat gtg act agt Ser Pro Leu Gly Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser  -35  -30  ggc tca tca tca cca gtg acc tgg ttg ggc cta ctc tcc ttc cag aac Gly Ser Ser Ser Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn	
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Agn Van Clar Clar han had the Wal Clar Was Was Was You Will Clar	542												
Asn Xaa Gly Gly Asp Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly 90 95 100 105													
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50

297

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345

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Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn Gly Pro Gly Thr	103
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<210> 363

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WO 99/31236

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-55 <b>-</b> 50 <b>-</b> 45	
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-	-1-
	tac 300
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Xaa Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val	Ile
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His Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala	Glu
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55 60 65	70
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Gly Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro	
	Add
7.5	E40
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Pro Leu Ser Val Thr Cys Thr Pro	
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50

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Arg Asn Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser	
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Gln Thr Gly His Met Arg Met Ala Ala Leu Leu Pro Gln	
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His	Ser 105	Asp	Asn	Pro	Ser	Gln 110	Leu	Ile	Trp	Thr	Ser 115	Ser	Arg	agt Ser	Ala	591
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Glu	Pro	Tyr	Ser	Ser 140	Ser	Lys	Tyr	Ala	Thr 145	Asp	Leu	Leu	Ser	gtg Val 150	Ala	687
Leu	Asn	Arg	Asn 155	Phe	Asn	Gln	Gln	Gly 160	Leu	Tyr	Ser	Asn	Val 165	gcc Ala	Cys	735
Pro	Gly	Thr 170	.Ala	Leu	Thr	Asn	Leu 175	Thr	Tyr.	·Gly	Ile	Leu 180	Pro	ccg Pro	Phe	783
Ile	Trp 185	Thr	Leu	Leu	Met	Pro 190	Ala	Ile	Leu	Leu	Leu 195	Arg	Phe	ttt Phe	Ala	831
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tgt	acat	tct :	ggggt	taca	tg ga	attt	ctac	t ga	gttg	gata	ata	tgcat	ttt	gtaa	taaact	1482
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gttgataagg cgcttgctga tgacttggaa aaaaacttcc caagtttgaa ggttcagact

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765

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<222> 1027..1040

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ata agt tot coa ott gta gaa ttt gta aaa gtt ttg tgc acc aac cag	286											
Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys Thr Asn Gln												
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gtt ctc att act gcc agg gct gtg cct aca aaa aag gca tct gtg cga	334											
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala Ser Val Arg												
-5 1 5												
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Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser Lys His Leu												
10 15 20 25												
tot aga tgt att gat gga att tot ggo ttt ota aat gat ttt act tto	430											
Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp Phe Thr Phe												
30 35 40												
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Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu												
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<221> polyA\_site <222> 1151..1162

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Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys	
-40 -35	
gaa tgt att gac tgg agt gag aga aga aat gct gtg gca tct gtt gtc	158
Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val	

	-30					-25					-20					
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			Leu													•
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			cct													254
Val	Val	Tyr	Pro	Lys	Pro	Glu	Gln		Asn	His	Ala	Phe		Thr	Cys	
			5					10					15	+ 00	224	302
			tcc Ser													302
GIY	Vai	20	ser	1111	Deu	Ald	25	PIIC	Mec	116	ASII	30	vai	Der	ASII	
act	caq		aga	aat	gat	agc		gaa	agc	qqċ	tat		qqa	aga	aca	350
			Arg													
	35		_		•	40	•			•	45		-	_		
			gtt													398
Gly	Ala	Arg	Val	Trp		Phe	Ile	Gly	Phe		Leu	Met	Phe	Gly		
50					55					60					65	
ctt	att	gct	tcc	atg	tgg	att	ctt	ttt	ggt	gca	tat	gtt	acc	caa	aat	446
Leu	Ile	Ala	Ser		Trp	Ile	Leu	Phe		Ala	Tyr	Val	Thr		Asn	
			tat	70	~~~	a+ -	~~+	~+ ~	75		~~~	226	<b>703</b>	80	ata	494
			Tyr													424
1111	Азр	Vai	85	PIO	Gry	Deu	AIG	90	FIIC	rnc	0111	Abii	95	Deu		
ttt	ttt	agc	act	cta	atc	tac	aaa		qqa	aga	acc	qaa	qag	cta	tgg	542
			Thr													
		100				-	105		Ī	_		110			<del>"</del>	
acc	tga	gatc	act	tctt	aagt	ca c	attt	tcct	t tt	gtta	tatt	ctg	tttg	tag		595
Thr																
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_					-	_	_	_		-		-			tatttt	715 775
															tgagta catcat	835
															tgcctg	895
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ctg cgc ttc ctg agg gct gac ggc gac ctg acg cta cta tgg gcc gag Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu Thr Leu Leu Trp Ala Glu -5 10	149
tgg cag gga cga cgc cca gaa tgg gag ctg act gat atg gtg gtg tgg Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu Thr Asp Met Val Val Trp  15 20 25	197
gtg act gga gcc tcg agt gga att ggt gag gag ctg gct tac cag ttg Val Thr Gly Ala Ser Ser Gly Ile Gly Glu Glu Leu Ala Tyr Gln Leu 30 35 40	245
tct aaa cta gga gtt tct ctt gtg ctg tca gcc aga aga gtg cat gag Ser Lys Leu Gly Val Ser Leu Val Leu Ser Ala Arg Arg Val His Glu 45 50 55	293
ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
aaa gat ata ctt gtt ttg ccc ctt gac ctg acc gac act ggt tcc cat Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His 75 80 85 90	389
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attotggtca acaatgtgga aatgtcccag cgttctctgt gcatggatac caacttggat	495
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kctgcctcac atgatcgaga ngaarcaagg aaagattgtt actgtgaata gcatcctggg	615
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	-95	ugue		Jucus		99			, -9:		-			-		_	1,0
Met Ser Gln Arg Ser Leu Cys -60																	
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				Ser													
•	-55	-				-50			_		-45					-40	
	tta	ġgg	acg	gtg	tcc	ttg	aca	aaa	tgt	gtt	ctg	cct	cac	atg	atc	gag	271
	Leu	Gly	Thr	Val	Ser	Leu	Thr	Lys	Cys	Val	Leu	Pro	His	Met	Ile	Glu	
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	Arg	Lys	Gln	Gly	Lys	Ile	Val	Thr	Val	Asn	Ser	Ile	Leu	Gly	Ile	Ile	
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	Ser	Val	Pro	Leu	Ser	Ile	Gly	Tyr	Cys	Ala	Ser	Lys	His	Ala	Leu	Arg	
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	ata	gtt	tct	aac	att	tgc	cca	gga	cct	gtg	caa	tca	aat	att	gtg	gaa	463
	Ile	Val	Ser	Asn	Ile	Cys	${\tt Pro}$	Gly	Pro	Val	Gln	Ser	Asn	Ile	Val	Glu	
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	aat	tcc	cta	gct	gga	gaa	gtc	aca	aaa	act	ata	ggc	aat	aat	gga	aac	511
	Asn	Ser	Leu	Ala	Gly	Glu	Val	Thr	Lys	Thr	Ile	Gly	Asn	Asn	Gly	Asn	
				45					50					55			
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	Gln	Ser	His	Lys	Met	Thr	Thr	Ser	Arg	Суѕ	Val	Arg	Leu	Met	Leu	Ile	
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		Leu	Val	Thr	Tyr		Trp	Gln	Tyr	Met		Thr	Trp	Ala	Trp		
	90					95					100					105	
				aag	_		_							_	_		703
	Ile	Thr	Asn	Lys		Gly	Lys	Lys	Arg		Glu	Asn	Phe	Lys		Gly	
	1				110					115					120		
		-	-	rac								_				-	751
	Val	Asp	Ala	Xaa	Ser	Ser	Tyr	Phe	-	Ile	Phe	Lys	Thr	Lys	His	Asp	
				125					130					135			
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				-		-		-	-		_	_				atagat	871
	_		_			tg g	rrtga	aaata	a aaa	aaata	aaat	aata	aaaa	gat 1	tgcca	atgrrt	931
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153

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249

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345

393

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489

537

585

621

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-25

105

-10

55

70

150

85

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Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly Phe Ile Thr Phe

gat ata act gct gat cta gag aat ata ttt gat tgg aat gtt aag cag Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp Asn Val Lys Gln

ttg ttt ctt tat tta tca gca gaa tat tca aca aaa aat aat gct ctg

Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys Asn Asn Ala Leu

aac caa ktt gtc cta tgg gac aag att gtt ttg aga ggt gat aat ccg Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg Gly Asp Asn Pro

aag ctg ctg ctg aaa gat atg aaa aca aaa tat ttt ttc ttt gac gat Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe Phe Phe Asp Asp

gga aat ggt ctc wag gga aac agg aat gtc act ttg acc ctg tct tgg

Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu Thr Leu Ser Trp 115 aac gtc gta cca aat gct gga att cta cct ctt gtg aca gga tca gga

Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val Thr Gly Ser Gly

cac gta tot gto coa ttt coa gat aca tat gaa ata acg aag agt tat

His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile Thr Lys Ser Tyr

100

50

130

145

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65

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15

.95

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<400> 378

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<210> 380 <211> 82 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1

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Val Pro Leu Ile Ile Val Asn Ser Ile Ala Ile Val Leu Leu Leu
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Phe Gly

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175

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                                       ~45
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                                   -30
                                                      -25 ·
Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser
           -20
                              -15
Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu
                           1
Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr
                                       20
Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro
               30
                                   35
Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr
           45
                               50
Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe
                           65
Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile
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Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala
                  95
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<220>
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<211> 27
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Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn 5 10

<210> 386 <211> 186 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 386 Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile -10 -15 Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp 20 Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro 35 30 Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly 50 Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys 70 65 Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser 85 Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu 100 Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly 115 110 Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser 130 135 Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile 145 Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser 160

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<210> 387
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 387
Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu
                        -20
                                            -15
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
                    -5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                    60
                                        65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                    80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                                95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                            110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                       125
                                            130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
135
                    140
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                    -50
                                         -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
                                     -30
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                                 -15
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
                                        20
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
```

Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
45
50
55
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala

<210> 389

<210> 390 <211> 149

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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser 75 80 85

Pro Gly Cys Tyr Arg Tyr 90 95
```

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<211> 236
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 389
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
                                       -20
                      -25
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
                                    - 5
                 -10
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Ser Leu Phe Asp Leu
                           10
          5
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                         25
Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                                         45
                      40
Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                                     60
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
                                 75
              70
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
                                                95
                             90
          85
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
                                    110
                         105
     100
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
                                      125
                  120
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
            135
                                    140
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
            150
                                  155
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                              170
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
                          185
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
                     200
```

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<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -100..-1

<400> 390
Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
-100 -95 -90 -85
```

Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr -75 -70 -80 Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile -55 -60 Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp -40 -50 -45 Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn -25 -30 Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met -10 -15 -20 Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile 5 10 Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val 25 20 Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro 35 Gly Tyr Leu Met Gly

<210> 391 <211> 69 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -49..-1

<210> 392 <211> 241 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1 <400> 392

Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn -30 -25 -20 -15

Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val -10 -5 1

Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr 5 10 15

Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr 20 25 30

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Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 . 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 125 120 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 155 150 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln . 170 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 200 205 : 210 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -30..-1

<400> 393

 Met Asn Cys Asn Val Val Ser Glu Arg Gly Lys Trp Leu Glu Val Glu

 -30
 -25
 -20
 -15

 Cys Ser Leu Met Thr Cys Thr Thr Leu Ile Asn Ala Ser Ala Ile Ser
 -10
 -5
 1

 Thr Asn Thr Leu Thr Asp Met Gly Ser Phe Asp Arg Arg Glu Ser
 5
 15

<210> 394 <211> 65 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -28..-1

\_30

35

Ser

<210> 395

<211> 73

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro
-20
-15
-10

Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys
-5 5

Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 10 15 20

Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 25 30 35 40

Trp Gly Gln Gly Thr His Ser Ser Leu

45

<210> 396

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 396

Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr
-15 -10 -5

Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu
1 5 10

Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 15 20 25 30

Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala

<210> 397

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -93..-1

<400> 397

Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn
-90
-85

Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val

```
-70
Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr
                       -55
Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val
                   -40
                                      -35
Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn
                                  -20
Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu
                              -5
Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu
                                         15
                      10
Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys
                  25
                                      30
Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly
                                  45
Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn
                              60
Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys
                          75
Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln
                90
```

<210> 398 <211> 149 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 -45 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -35 -30 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 -20 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 35 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 50 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu

<210> 399 <211> 73 <212> PRT <213> Homo sapiens

Phe Ser Met Val Gly 75

```
<220>
<221> SIGNAL
<222> -20..-1
```

<400> 399

Met Thr Pro Leu Leu Thr Leu Ile Leu Val Val Leu Met Gly Leu Pro -15 -10 Leu Ala Gln Ala Leu Asp Cys His Val Cys Ala Tyr Asn Gly Asp Asn 1 5 10 Cys Phe Asn Pro Met Arg Cys Pro Ala Met Val Ala Tyr Cys Met Thr 20 25 Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met Lys Val Ser Lys Ser Cys 35 Val Pro Arg Cys Phe Glu Xaa Cys Val

50

<210> 400 <211> 86 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -20..-1

<400> 400

Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly -15 -10 Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe 5 Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala 15 20 25 Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu 35 40 Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly 50 Pro Xaa Lys Leu Arg Gln 65

<210> 401 <211> 78 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 401

Met Cys Pro Val Phe Ser Lys Gln Leu Leu Ala Cys Gly Ser Leu Leu -20 -15 -10 Pro Gly Leu Trp Gln His Leu Thr Ala Asn His Trp Pro Pro Phe Ser -5 Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser Glu Gln Ile Ser Glu 15 20 Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg Ser Leu Asn Gln Glu 35 Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr Ser Ile Thr

. . .

.45

50

55

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<210> 402
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 402
Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser
       -25 -20 -15
Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
                        -5
Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro
                         15
          10
Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg
Thr
<210> 403
<211> 211
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<210> 403 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<400> 403 Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr

Phe Phe Ser Gly Val. Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe -5 Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly 10 15 Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 30 Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His 50 45 Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 65 60 Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 75 80 Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 95 90 Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu 115 110 Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys 125 130 Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln 135 140 145 Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 150 . 155 160 Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr 170 175

-20

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Arg Ser Ile

<210> 404 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1 <400> 404 Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp -75 -70 Ser Val Arg lle Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr .-60 -55 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -40 -45 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -30 -25 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -15 -10 -5 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 1 5 . 10 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 20 25 -

Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu

<210> 405 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1

<400> 405

35

Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile -20 -15 Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro -5 1 Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu 10 15 Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu 25 30 Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His 40 45 50 Ala His Trp Xaa Ser Xaa

<210> 406 <211> 162 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -31..-1
<400> 406
Met Ala Ala Arp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                              - -20
                  -25
Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
                  -10
                                     -5
Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
                              10
Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
                         25
Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
                  40
                                       45
Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
      55
                                    60
Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
                                  75
           70
Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                             90
Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
                          105
Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
                      120
                                         125
Pro Asn
130
```

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<210> 407
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
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<400> 407 Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile -30 Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe -20 · -15 -10 Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu 1 Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln 20 15 Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu Tyr Leu Leu Leu Gly 35 Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met Val Arg 60

<210> 408 <211> 70 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
       -10
                        -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
                            10
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                       25
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
             40
Asp Phe Ser Ser Phe Thr
50
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
                 -40
                                    -35
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
             -25
                                -20
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
        -10
                            -5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
                     10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
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<210> 411 <211> 51 <212> PRT

-10

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
           -20
                               -15
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
                          1
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
                   15
                                        20
10
Ile Trp Pro
```

<210> 412 <211> 95 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1

<400> 412 Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr -45 -40 Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn -25 -20 -30 Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser -10 -5 Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys 10 Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu 25 Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val

40

<210> 413 <211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1

35

<400> 413 Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly -25 -20 Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys -10 -5 Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser 5 10 Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser 20

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<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
              -75
                               -70
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
                              -55
           -60
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
       -45
                          -40
                                            -35
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
                       -25
                                          -20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
                -10
                                   -5
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
                            10 15
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe
                          25
                                            30
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
                      40
                                         45
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
                  55
                                      60 .
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
              70
                                 75
His Tyr Ile Arg His Ala Arg Gly Gly Leu
           85
```

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<210> 415
<211> 190
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
<400> 415
Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe
                           -75
                                              -70
His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly
                       -60
                                           -55
Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile
                   -45
                                       -40
Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln
               -30
                                   -25
Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr
           -15
                               -10
                                                   - 5
Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile
                       5
                                           10
Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile
                  20
                                       25
Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu
                                   40
```

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 416

Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -60 -55 -50 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -30 . -40 -35 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu · -15 -25 -20 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 25 30 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser 45 40 . Ser Lys

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -108..-1

<400> 417 Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -100 -95 -105 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu -85 -90 -80 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -70 -65 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -55 -50 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -40 -35 -30 Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -25 -20 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser

<210> 418 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 418 Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu -15 -10 Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val 15 20 Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro 35 Leu Arg Met

<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1

45

<400> 419 Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -30 -25 . . -20 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -15 -10 -5 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val 10 Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu 25 Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser 40 45 Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe 55 60 Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 70 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 85 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser 100 105

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 120 125 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 135 140 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 170 165 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 185 180 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 200 205 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Gly Glu Val Ile Gly Val Leu Trp 235 230 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 250 245 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 290 295

<210> 420 <211> 65 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -19..-1

<400> 420

Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His
-15 - 15 - 10 - 10 - 5 - 5

Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His
1 - 10 - 10 - 10

His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn
15 - 20 - 25

Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val
30 - 35 - 40 - 45

<210> 421 <211> 57 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

```
-10
                                   - 5
Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
                        10
Glu Glu Gln Lys Xaa Ser Gly Ile Met
<210> 422
<211> 85
-<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 422
Met Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
       -15
                          -10
Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser
   1
                5
                                       10
Asp Ser Asp Glu Leu Ala Ser Gly Xaa Phe Val Phe Pro Tyr Pro Tyr
               20
                                  25
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
           35
                               40
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
Leu Pro Ser Glu Lys
   65
<210> 423
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
Met Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
      -15
                           -10
Gly Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser
    1
                   5
Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr
                20
                                   25
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
                               40
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
Leu Pro Ser Glu Lys
    65
<210> 424
<211> 69
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<212> PRT <213> Homo sapiens <210> 425 <211> 122

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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
             -25 -20 -15
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
                           -5
         -10
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                 10
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                                   30
           25
Gln Xaa Ala Leu Leu
```

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
                     -50
                                -45
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
                                    -30
           -35
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
              -20
                                -15
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
                            1 5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
                                       20
                     15
   10
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
                                    35
                 30
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
                                50
```

45

60

Val Pro Ser Trp Val Gln Phe Phe Leu Gly

```
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly
                                      -20
               -25
Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln
               -10
```

```
Arg Cys Ser Gly Ser Pro Leu Pro Leu
5 10
```

<210> 427 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1 <400> 427 Met Ala Pro His Thr Ala Ser Phe Gly Val Cys Pro Leu Leu Ser Val -30 -25 Thr Arg Val Val Ala Thr Glu His Trp Leu Phe Leu Ala Ser Leu Ser -15 -10 Gly Ile Lys Thr Tyr Gln Ser Tyr Ile Ser Val Phe Cys Lys Val Thr 1 5 Leu Ile

<210> 428 <211> 136 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 428

Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala -15 -10 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg . 20 25 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Leu Ala Thr Leu 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 50 Met Val Gly Gly Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 85 90 Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 95 100 105 Met Pro Gly Leu Ser Gly Val Leu 115

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>

<221> SIGNAL <222> -65..-1

<400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 -55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 -30 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp 40 Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 55 60 Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 75 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 85 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 105 110 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120 Val Ser

<210> 430 <211> 141 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -69..-1

<400> 430

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -50 -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -30 -25 -35 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -10 -15 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser ٠ ٦ Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 20 25 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 35 40 Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly 65

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
                -65
                                    -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
            -50
                                -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
        -35 🔻
                           -30
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                       -15
                                         -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
                  1
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Ile
           15
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
       3.0
                           35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                       50
                                           55
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                   65
                                       70 -
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
                                   85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
           95
                               100
                                                   105
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
                           115
                                               120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                      130
                                           135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
                                      150
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
               160
Gly Tyr Glu Glu Leu Leu Thr Ser
            175
```

Phe

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<210> 433
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
```

<210> 434 <211> 144

<400> 433 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -5 -10 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 . 15 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 20 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 60 His Arg Ile Cys Asp Leu 70

-318-

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 434
Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile
                              -50
Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro
                          -35
Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu
                      -20
                                         -15
  -25
Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val
-10 -5
                                    1
Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu
        10
                             15
Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala
                         30
Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp
                      45
Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu
                  60
                                     65
Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser
```

<210> 435 <211> 121

OF THE SAME

```
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 435
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                       -10
                                 -5
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                  10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
         20
                               25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
                          40
Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                      55
                                      60
Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                                   75
Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
              85
Leu Gly Ser Gly Glu His Pro Xaa Xaa
           100
```

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<210> 436
<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 436
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
           -10
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                 10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
         20
                            25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys
                         40 . 45
Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                                        60
Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
               85
                                 90
Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln
                             105
Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                       120
                                             125
Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
          135
Glu Gly
145
```

<210> 437

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```
<211> 110
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 437
Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
                   -15
                                        -10
Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
               1
Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
        15
                            20
Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                                           40
                       35
Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
45
                    50
                                        55
Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                65
                                    70
Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
            80
                                85
<210> 438
<211> 71
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 438
Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                   -10
                                        -5
Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                                10
Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                            25
                                                30
Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
                       40
Gln Val Pro Arg Arg Ala Gly
<210> 439
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 439
Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
                -20
                                    -15
```

<210> 440

```
      Ser
      Leu
      Asn
      Thr
      Leu
      Leu
      Leu
      Gly
      Gly
      Val
      Asn
      Lys
      Ile
      Ala
      Glu
      Lys

      Ile
      Cys
      Gly
      Asp
      Leu
      Lys
      Asp
      Pro
      Cys
      Lys
      Leu
      Asp
      Met
      Asn
      Phe
      Gly

      Ser
      Cys
      Tyr
      Glu
      Val
      His
      Phe
      Arg
      Tyr
      Phe
      Tyr
      Asn
      Arg
      Thr
      Ser
      Lys

      Arg
      Cys
      Glu
      Thr
      Phe
      Val
      Phe
      Ser
      Ser
      Cys
      Asn
      Gly
      Asn
      Leu
      Asn
      Asn
      Asn

      Phe
      Lys
      Leu
      Lys
      Ile
      Glu
      Arg
      Glu
      Val
      Xaa
      Cys
      Val
      Ala
      Lys
      Tyr
      Lys

      Phe
      Pro
      Arg
      France
      France
```

```
<211> 169
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 440
Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
                   -20
                                     -15 -10
Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                       30
Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                   45
                                       50
Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
                                   65
Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
           75
Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
                          95
Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
                       110
                                         115
Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
                   125
                                     130
Arg Thr Pro Asp Leu Pro Ala Leu Ala
```

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 ~50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -35 -40 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -25 -20 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 25 30 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 Tyr Ser Thr Lys Arg Ser Pro 90

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 442

 Met
 Ile
 Leu
 Cys
 Phe
 Leu
 Leu
 Pro
 His
 Arg
 Leu
 Glu
 Ala
 Arg

 -15
 -10
 -10
 -5
 -5
 -6
 1
 1

 Glu
 Ile
 <

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1

<400> 443

Met Ser Trp Thr Val Pro Val Val Arg Ala Ser Gln Arg Val Ser Ser
-30 -25 -20

Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu Cys Pro Arg Gln
-15 -10 -5

Ala Thr Arg Ile Pro Leu Asn Gly Thr Trp Leu Phe Thr Pro Val Ser
1 5 10 15

```
Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
                                40
Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                    70
Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                   85
                                90
Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
                100
                                  105
Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
                               120
Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
        130
                            135
Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                       150
Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                   165
                                       170
Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
               180
                                   185
Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
                               200
Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
                           215
Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
                       230
                                           235
Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                   245
                                      250
Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
                260
                                   265
Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
           275
                               280
Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                           295
Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                      310
                                          315
Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
                   325
                                      330
Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
                340
```

```
<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                            -30
                                                -25
     -35
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                                            -10
                        -15
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                                    5
-5
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                        -20
                                            -15
   -25
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                   -5
                                        1
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
                                15
           10
Thr Arg Gly
       25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447 -
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
-30
                    -25
                                        -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro
                                     -5
                -10
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
        5
                            10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                        25
                                            30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn 75 Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln 90 Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu 105 110 Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His 120 125 Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg 135 140 Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu 150 155 Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr 170 175 His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg 185 190 Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg Gln Leu

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 448

ti i sekantalia etament ti kun mendeban aminguti metra semendapan terminak asang ang metop, untuk jumungga, a

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -55 -50 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -20 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -5 · Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75 Pro Glu Phe His Ile Glu Ile Leu Ser Ile

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

20

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
              -55
                              -50
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                  -40
                                    -35 .
-45
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
              -25
                         -20
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
          -10 -5
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
            10
His Pro Cys Ala Thr Tyr Pro Pro Xaa
                 25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 450
Met Arg Met Ser Leu Ala Gln Arg Val Leu Thr Trp Leu Phe Thr
                     -20
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
                  - 5
                                   1
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
                                         . 20
    10
                            15
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
   25
                         30
Phe Asp Leu Asp Met Asp His Thr Ile
   40
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -34..-1
<400> 451
Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser
              -30
                                 -25
Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser
                            -10
          -15
Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys
      1
Ala Ile Ile Leu Met Lys
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<210> 452

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<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
                                ~30
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
                            -15
                                               -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
                       1
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
                15
                                   20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
            30
                                35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
                            50
Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                       65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
```

<210> 453 <211> 166 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1 <400> 453 Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile -30 Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu -15 -10 Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe 15 20 Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn 35 Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His 50 55 Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His 85 Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg 100 105 Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu 110 115

Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg -5 1 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 15 10 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 50 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 80 75 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 110 115

<210> 455 <211> 91 <212> PRT <213> Homo sapiens

Arg Asn Trp Glu

<220>
<221> SIGNAL
<222> -64..-1

Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His

Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg

. 130

145

125

25

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa
           -20
                               -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
                           1
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                   15
                                       20
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
               30
                                  35
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                           65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                       80
                                          85
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                   95
                                      100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
               110
                                   115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
           125
                               130
                                                   135
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                           145
                                              150
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                      160
                                          165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
                  175
                                      180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
               190
                                  195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
                              210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                           225
Xaa
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<210> 457 <211> 193 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 457

Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro
-60 -55 -50 -45

Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -40 -35 Leu Leu Cly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -20 -25 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -10 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 25 30 Val Gly Pro Thr Pro Gly Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 90 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 105 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 125 Glu

<210> 458 <211> 107 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg
-25 -20 -15

Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser
-10 -5 1

Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile
5 10 15 20
Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys

Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys

25

30

35

Val Clu Dha Yan Chu Chu Can Tha Dan Lun Dun Tha Lla Clu Val

Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val 40 45 50

Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu
55 60 65

Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly
70 75

<210> 459
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1

<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -10 -5 Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 10 15 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys 25 - 30 Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr 40 45 Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 75 80 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn 100

<210> 460 <211> 44 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 460 Met Lys Val Gly Val Leu Trp Leu Ile Ser Phe Phe Thr Phe Thr Asp -15 -10 -5 Gly His Gly Gly Phe Leu Gly Val Ser Trp Cys Tyr Val Ser Tyr Leu 10 Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg Ile 20

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 461

Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -10 -5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 15 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 45 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 60 65 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser 70 75 Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

90

95

<210> 462 <211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

<400> 462

Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -35 -30 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu -5 1 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 10 15 20 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 35 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 45 50 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 65 Asp Asn Pro Arg Val Lys Ala Ala Leu Ala Ser Leu Lys Lys Tyr 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 95

<210> 463 <211> 232 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -25 -20 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -10 -5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 10 15 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 25 30 Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 45 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 55 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly 75 Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 90 95 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

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105
                                          110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
                 120
                                     125
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
              135
                                 140
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
                    . 155
          150
                                        160
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
                         170
                                   175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
                      185
Val Lys Cys Lys Phe Leu Tyr Asn
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
                      -15
                                         -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
                   1
                                 5
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
           15
                           20
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
                           35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
               -15
                               -10
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
                          5
Gly Arg
   15
<210> 466
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<212> PRT <213> Homo sapiens <220>

<211> 215

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<221> SIGNAL <222> -54..-1
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<400> 466

Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -50 -45 -40

Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu
-35 -30 -25

Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -20 -15 -10

Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp
-5 1 5 10

Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser 15 20 25

Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 30 35 40

Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe
45 50 55

Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 60 65 70

Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 75 80 85 90

Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu
95 100 105

Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 110 115 120

Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 125 130 135

Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 140 145 150

Ile Ile Arg Lys Cys Phe Ile

<210> 467

<211> 27

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1

<400> 467

Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr Ser Lys Arg
-15 -10 -5

Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe 1 5 10

<210> 468.

<211> 85

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 468

Met Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu **-15** -10 -20 Phe Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys · - 5 1 Phe Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser 15 Leu Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe 30 35 Pro Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa 45 50 :Tyr Trp Asp Asn Leu 60

<210> 469 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

<210> 470 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1

 400> 470

 Met Thr Pro Gln Tyr Leu Pro His Gly Gly Lys Tyr Gln Val Leu Gly -40
 -35
 -30
 -30

 Asp Tyr Ser Leu Ala Val Val Phe Pro Leu His Phe Ser Asp Leu Ile -25
 -20
 -15

 Ser Val Leu Tyr Leu Ile Pro Lys Thr Leu Thr Thr Asn Thr Ala Val -10
 -5
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 5

 Lys His Ser Ile Gln Lys Asn Cys Met Xaa Leu Val Leu Gly Lys Leu 10
 15
 20

 Leu Ser Gln
 -10
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<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -71..-1

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<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
                   -10
                                -5
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                               10
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
       20
                          25
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
                       40
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 472
Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His
                                -50
Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu
                           -35
                                               -30
Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile
                       -20
                                           -15
Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala
                   -5
                                       7
Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly
          10
                               15
Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile
                           30
Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa
                        45
Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser
                   60
                                       65
His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro
              75
                                   80
Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys
                               95
Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly
                           110
Gln Val Asn
    120
<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
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<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
             -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                   -50
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
               -35
                                  -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
                               -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                   15
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
               30
                                   35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                               50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
                           65
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                       80
                                           85
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
                   95
                                       100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
              110
                                  115
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
           125
                              130
                                                 135
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
       140
                          145
                                              150
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
   155
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<210> 474 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

<400> 474

Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe -30 -25 Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile -20 Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe 5 Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu 15 20 Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val 35 Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn 50 Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 65 70 His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr 80 85 Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe The second of th

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100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly .
                                       120
                    115
  110
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
                      130
 125
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
                                          -10
                       -15
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
-5
                   1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                             20
           15
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
       30
                           35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
                                -15
             -20
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
           -5
                             1
Val Leu Gly Val Phe Phe Pro Ile Leu
    10
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL <222> -27..-1

<400> 477 Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu -20 Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu 10 15 Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn 30 Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys 4.0 45 Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys 60 65 Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser

<210> 478 <211> 250 <212> PRT <213> Homo sapiens

225

<221> SIGNAL <222> -18..-1

<400> 478

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -10 Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser 10 Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 145 150 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

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<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                                           -10
                       -15
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
                                    5
                   1
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
           15
                               20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                           35
                                               40
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                                           55
                       50
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                   65
                                       70
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
               80
                                    85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                               100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
       110
                          115
Gly Lys Val Lys Ser Phe Lys
   125
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
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-20 -15 Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe 1 Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg 15 20 10 Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe 30 35 Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu 45 Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys 65 Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala 75 80 Gly Arg Gln Gln Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa 95

Asn Asn Asn Arg Asp Leu Ser Met. Val Arg Met Lys Ser Met Phe Ala 105 110 115 Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ilė Phe 125 130 Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa 140 145 Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys 160 Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn 170 . 175 Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln 185 190 195 Ala Gly Gly Phe Leu Gly Pro Pro Pro Pro Ser Gly Lys Phe Ser

<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1

<400> 481 Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -20 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -10 -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 15 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys . 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Ala 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

<220>

and the control of th

<221> SIGNAL <222> -39..-1

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -30 -25 -35 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -15 -20 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val 1 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala

35 30 Arg Leu Leu Thr His Trp

45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -20 -15

Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 - 5

Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly -10 -5 Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 10 Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 20 25 Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala

Thr

<210> 485

<211> 130

e of Audition Datable and All Professional Acceptance (All Audition Acceptance) and Audition Acceptance (All Auditor Acceptance) and Auditor (All Auditor Acceptance) and Aud

<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1 <400> 485 Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu -50 Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg -30 -25 -35 Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile -10 -15 Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr 5 -5 1 Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val 20 10 15 Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa 35 30 Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg 50 45 Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp 65 Ala Leu 75 <210> 486 <211> 209 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -84..-1 <400> 486 Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu -75 -80 Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr -60 Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly -45 -40 Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu -25 -35 -30 Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu -10 -15 Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr 5 1 Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly 25 20 Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val 35 Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His

50

55

70

Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa

Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg 80 85 90 Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr (C) 清於 (表演者等)

The target of the second of th

```
100
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
      -15 -10
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                  5
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
               -25 -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
                           -5
           -10
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
   5
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
               -45
    -50
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
               -30
                                        -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                 -15
```

Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala

```
10
Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly
                           20
Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp
                       35
Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg
                   50
                                       55
His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro
                                   70
Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser
           80
                             85
Met Pro Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa
                           100
       95
Thr Arg Ser
   110
```

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<210> 491 <211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 491

<222> -50..-1

Met His His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala -30 -25 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 -5 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser 5. Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 15 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln 35 40 Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

50 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp 85 Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 120 115 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 135 130 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln

<210> 492 <211> 216 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -15..-1

Met Val Cys Val Leu Val Leu Ala Ala Ala Ala Gly Ala Val Ala Val -5 -10 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 70 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 100 105 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly 140 135 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 155 150 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 Ser Val Tyr Leu Gly Arg Ile Val

<210> 493
<211> 134
<212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 493
Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly
                -15
                                   -10
Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr
Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala
                       20
                                           25
Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile
                  35
                                       40
Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro
         . 50
                                   55
Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg
           65
                               70
Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu
                           85
Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly
Asp Glu Val Lys Lys Glu
110
<210> 494
<211> 85
<212> PRT
<213> Homo sapiens
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a dina mendahan serika mendahan merenggi bermasahan dinaman persembahan mengan persembahan mengan bermasahan dinaman serikan mengan bermasah dinaman serikan persembahan dinaman serikan persembahan perse Persembahan persemb

<210> 495 <211> 292 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

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<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
                                   -20
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
                              -5
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                      10
                                          15
Leu Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr
                  25
                                      30
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
                                  45
              40
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                              60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
                                             80
                          75
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
                      90
                                          95
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
                  105
                                     110
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
                                   125
              120
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
           135
                               140
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                           155
                                               160
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu
                       170
                                           175
Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
180
                   185
                                      190 .
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
               200
                                   205
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
                              220
                                                  225
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
                          235
                                              240
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
                      250
Lys Lys Gln Glu
260
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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
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<221> SIGNAL <222> -56..-1

<220>

<400> 496 Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser -50 -45 Cys Ser Arg Ser Arg Lys Arg Gln Thr Arg Arg Arg Arg Asn Pro Ser -35 -30 Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro -20 -15 Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu Thr Gly 1 Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala Gly Pro 10 15 20

```
Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 25 30 55 40

Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 45 50 55

Ala His Pro Lys Val Leu Lys Val Ala Leu 60 65
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<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28...1

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 10 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 25 30 Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 45 40 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 60 65 Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu Leu Gly 70 Arg Gln Leu 85

<210> 499 <211> 99 <212> PRT <213> Homo sapiens WO 99/31236

<220> -<221> SIGNAL <222> -13..-1

<400> 499

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro -5 Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 15 10 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 30 25 Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 45 40 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 60 55 Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly 75

kandisella, silika taun salam ang limpa ang mangang lindi salas salang ang salas salas salah da na salas salas sanang mangang ang salas s

<210> 500 <211> 108 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -25..-1

Arg Gln Leu 85

<400> 500 Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala -15 -20 Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His 10 20 15 Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 30 35 Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe 45 50 Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp 65 60 Asn Val Gly Pro Leu Ile Ile Lys Lys Glu Thr

<210> 501 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

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10
Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                            25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                        40
                                            45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
                                        60
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
           85
                                90
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
                            105
                                                110
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
                       120
                                            125
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
                   135
                                       140
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
               150
Thr Gly Gln Asp Phe Lys Glu
           165
```

<210> 502
<211> 98
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -15..-1

<400> 502
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp

<210> 503 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -57..-1

<400> 503
Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn
-55
-50
-45

Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 -30 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -15 -20 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn -5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His 30 35 Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 45 50 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly 60 65 Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 75 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 95 100 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro

<210> 504 <211> 140 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -14..-1

<400> 504 Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -10 -5 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 25 30 Leu Ser Met Pro Tyr Met Thr Arg Glu Gln Glu Arg Gly His Ala Ala 45 40 Leu Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 60 55 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 95 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 105 110

Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr 115 120 125

<210> 505 <211> 59 <212> PRT <213> Homo sapiens

<220>

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<221> SIGNAL
<222> -14..-1
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<400> 505

Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His -10 ~5

Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn 15 10

Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr 25 30

Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 40

<210> 506

<211> 101

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -36..-1

<400> 506

Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg -25 -30

Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile -15 -10 .

Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg 1 5 10

Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys 15 20

Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly .35 40

Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa

Ala Ala Ser Xaa Gln

65

<210> 507

<211> 341

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -55..-1

<400> 507

Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu -50 -45

Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys -30

-35 Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu

-15 Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

1 5

Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg 15 20

Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn 35 Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys 50 Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp 65 Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe 80 · 85 Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser 95 100 Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys 120 115 110 Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro 135 130 Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn 150 145 Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly 160 165 Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp 180 175 Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala 190 195 Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe 215 210 His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala 230 220 225 Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu 245 240 Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu 250 255 260 265 Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu 275 Ser Gly Ser Cys Leu

<210> 508 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -42..-1

<400> 508 Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile -5 1 Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 15 10 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys 30 Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu 45 50 Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu 60

<213> Homo sapiens

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<210> 509
<211> 80
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 509
Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys
                       -20
                                           -15
Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala
                   -5
                                       1
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
          10
                               15
Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
                            30
                                               35
Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
   40
<210> 510
<211> 158
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
                                    -35
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
           -25
                               -20
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                           -5
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
                  10
                                       15
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
               25
                                   30
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
                               45
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                           60
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
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Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
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Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
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Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
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Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
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                                        50
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
                                   65
Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
Gly Asp Asn Pro Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
                           95
                                        .. 100
Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
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                                           115
Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
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 Leu
 Pro
 Pro
 Pro
 Leu
 Thr
 Asp
 Pro
 Arg
 Leu
 Ala
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770

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